CADTH

CADTH COMMON DRUG REVIEW

Clinical Review Report

Nitisinone (Orfadin)

(Sobi Canada Inc.)

Indication: For the treatment of patients with hereditary tyrosinemia type 1 in combination with dietary restriction of tyrosine and phenylalanine

Service Line:	CADTH Common Drug Review
Version:	Final
Publication Date:	April 2018
Report Length:	50 Pages

CADTH

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

CADTH

Table of Contents

CADTH

Tables

Figure

CADTH

Abbreviations

AE	adverse event
AFP	alpha-fetoprotein
CDR	CATH Common Drug Review
CLF	Canadian Liver Foundation
CORD	Canadian Organization for Rare Disorder
FAH	fumarylacetoacetate hydrolase
HCC	hepatocellular carcinoma
HT-1	hereditary tyrosinemia type 1
MAA	maleylacetoacetate
MCID	minimal clinically important difference
SA	succinylacetone
SAA	succinylacetoacetate
SAE	serious adverse event
WDAE	withdrawal due to adverse event

Drug	nitisinone (Orfadin)
Indication	Treatment of patients with hereditary tyrosinemia Type-1 in combination with dietary restriction of tyrosine and phenylalanine
Listing Request	As per indication
Dosage Form(s)	2 mg, 5 mg, 10 mg, and 20 mg capsules
NOC Date	December 13, 2016
Manufacturer	Sobi Canada Inc.

Executive Summary

Introduction

Hereditary tyrosinemia type-1 (HT-1) is a rare, autosomal recessive disorder of amino acid metabolism. The deficiency of fumarylacetoacetate hydrolase (FAH), which is the last enzyme in the pathway of tyrosine catabolism, results in the accumulation of toxic metabolites in the FAH-deficient hepatocytes and proximal renal tubular cells, and subsequently leads to liver and kidney damage. HT-1 typically manifests in infancy and is characterized by elevated plasma tyrosine levels. Liver dysfunction, such as bleeding abnormalities, hypoglycemia, ascites, edema, vomiting, irritability and jaundice, is the dominant clinical manifestation in children who are not detected by the newborn screening. Progression of the liver disease can be chronic or acute, with rapid deterioration. The lifetime risk of developing hepatocellular carcinoma (HCC) is as high as 37% in survivors without treatment, according to previous research. Many patients also suffer from neurocognitive deficits. The prevalence of HT-1 ranges from one in 12,000 to one in 100,000 individuals of Northern European descent. In Canada, a higher prevalence (one in 1,846 live births) was observed in the Saguenay–Lac-Saint-Jean region in Quebec. If untreated, the survival in patients with HT-1 is less than 12 months of life; most of these children die as a result of liver failure and severe coagulopathy.

Newborn screening allows for earlier identification of the disorder and earlier intervention. Previous research suggests better outcomes when treatment begins at an asymptomatic stage. Detection of succinylacetone (SA) in urine, plasma, or amniotic fluid is considered pathognomonic of tyrosinemia, as SA is not found in any other condition. Province-wide newborn screening for tyrosinemia has been practised since 1970 in Quebec.

Without treatment, death in childhood is common. Before the introduction of nitisinone, the management of HT-1 involved dietary restriction of phenylalanine and tyrosine and supportive treatment, until liver transplantation, if possible. At present, all affected children are managed with nitisinone in combination with a tyrosine- and phenylalanine-restricted diet. Liver transplantation remains the only definitive therapy for patients who do not respond to nitisinone therapy and there is progressive liver failure, or have suspected HCC.

However, liver transplantation is associated with risks of operative complications including death, graft rejection, and the challenge of organ availability.

Nitisinone (Orfadin) is a competitive inhibitor of 4-hydrooxyphenylpyruvate dioxygenase, an enzyme upstream of FAH in the tyrosine catabolic pathway. It prevents the accumulation of the catabolic intermediates, which can be converted to the toxic metabolites succinylacetone (SA) and succinylacetoacetate. The effect of nitisinone on inhibiting catabolism of tyrosine also leads to an increase in plasma tyrosine levels. Therefore, treatment with nitisinone requires restriction of the dietary intake of tyrosine and phenylalanine to prevent tyrosine toxicity.

Nitisinone (Orfadin) is supplied as capsules containing 2 mg, 5 mg, 10 mg, or 20 mg of nitisinone. An oral suspension formulation (4 mg/mL) was approved during the course of the CADTH Common Drug Review. However, this formulation is not assessed in the current review. Nitisinone (Orfadin) was provided to Canadian patients beginning in 1994 by Sobi, under the Health Canada Special Access Programme, which ended in late 2016. A Notice of Compliance for nitisinone for the treatment of adult and pediatric patients with HT-1 in combination with dietary restriction of tyrosine and phenylalanine was granted by Health Canada on December 13, 2016.[1] The recommended initial dosage of nitisinone is 1 mg/kg body weight per day, in two divided doses orally. The dose of nitisinone should be adjusted individually based on weight and biochemical and enzyme markers. The maximum daily dose of nitisinone is 2 mg/kg.

Results and Interpretation

Included Studies

Two manufacturer-submitted single-arm, open-label studies (NTBC and Quebec studies) were included in this review to assess the clinical efficacy and safety of nitisinone in combination with dietary restriction of tyrosine and phenylalanine in patients with HT-1. The NTBC study enrolled patients from 25 countries, including Canada (39 patients), between February 1991 and August 1997. In the main analysis of NTBC study, 207 patients received nitisinone at a starting dosage of 0.6 mg/kg/day to 1 mg/kg/day compared with a historical patient population that received dietary treatment alone (N = 108). A separate set of patients was subsequently enrolled, resulting in a complementary analysis performed on 250 patients who received nitisinone at the currently recommended starting dosage of 1 mg/kg/day. The outcomes assessed included: survival, survival without need for liver transplantation, death due to liver failure, development of HCC, porphyric crises as well as biochemical variables of liver function, kidney function, hemic system, SA, and tyrosine.

In the Quebec study, a cohort of 78 patients from Quebec born between 1984 and 2004 was analyzed. This period encompasses the introduction of nitisinone to Canadian clinical practice in 1994. Patients were categorized according to their treatment experience: nitisinone-naive, nitisinone started before 30 days of age, and nitisinone started after 30 days of age. Newborn screening, restricted diet and liver transplantation were available to all study participants, while patients in the nitisinone-treated groups also received nitisinone. Nitisinone was initially administered at 0.6 or 1 mg/kg/day, and it was increased to 1 mg/kg/day after the first few years of the study. Nitisinone-treated patients were compared with those who did not receive nitisinone therapy. Survival probability, occurrence of liver failure, requirement of liver transplantation, development of HCC,

porphyric crises, hospitalization due to acute HT-1-related complications, and biochemical variables related to HT-1 were examined.

The main limitation was that both studies were single-arm, and the clinical benefits and harms of nitisinone in combination with dietary restriction of tyrosine and phenylalanine were examined by comparing with a historical control. No formal statistical test was performed on the outcomes between treatment and control. No precise estimates of treatment effects of dietary restriction plus nitisinone relative to dietary restriction alone were produced. In addition, significant heterogeneity was observed between patients treated with nitisinone in combination with dietary restriction and the historical control (dietary restriction alone). Therefore, this renders it difficult to assess the benefit of nitisinone in combination with dietary restriction, although a protective effect is highly likely on a series of pre-specified clinically relevant long-term outcomes, such as survival and liver and renal function. However, given the nature of such a severe, life-threatening, rare disease, such a single-arm trial design seems acceptable, particularly in light of the lack of any other maintenance treatment.

Efficacy

Survival probability was higher in patients treated with nitisinone compared with patients with dietary restriction alone (historical cohort). In the NTBC study, the two-year and four-year overall survival rates for patients who initiated nitisinone at any age ranging from 0 to 24 months were 96% and 93%, respectively. For patients who started nitisinone before two months of age, their two-year and four-year overall survival rates were 88% and 88%, respectively. For those who started before six months of age, the two-year and four-year overall survival rates were 94% and 94%, respectively. For those who started after six months of age, the two-year and four-year overall survival rates were 97% and 93%, respectively. Results of the complementary analysis (i.e., at the recommended starting dosage of 1 mg/kg/day) were similar to those in the main analysis, the overall survival rate for patients who initiated nitisinone at any age was 93% at two years, four years and six years. In the historical population that received dietary treatment alone, the two-year survival rates were 29%, 74% and 96% for patients in whom symptoms developed before two months, from two to six months, and after six months of age, respectively. The four-year survival was similar to the two-year survival in the historical population, for all three subgroups of patients. In the Quebec study, higher survival rates were observed in patients treated with nitisinone (100%) compared with those who never received nitisinone treatment (71%) before liver transplantation.

Patients treated with nitisinone had a lower risk of death or transplantation due to liver failure. In the NTBC study main analysis, seven patients (3.4%) died of liver failure and seven transplantations (3.4%) were performed due to liver failure (i.e., 14 [6.8%] patients died or were transplanted due to liver failure). For patients whose treatment started before six months of age, 9% (seven of 80 patients) died of liver failure or were transplanted due to liver failure. In the historical control, 25% of patients died of liver failure and transplantation due to liver failure was performed in 6.4% of patients. According to the European Medicines Agency report, for patients in the historical cohort with symptom onset before six months, 42% died of liver failure or recurrent bleeding with or without liver failure (data were only reported with recurrent bleeding). The results imply that treatment with nitisinone reduces the risk of fatal liver disease in patients with the acute form of HT-1 presenting symptoms before six months of age. In the Quebec study, none of the patients who started

nitisinone before 30 days of age had developed detectable liver disease after more than five years of treatment.

Nitisinone-treated patients reported fewer liver transplantations (13%) compared with those who received dietary restriction alone (25%), in the NTBC study. In the Quebec study, more liver transplantations were performed for patients not treated with nitisinone (71%), compared with those who received nitisinone after 30 days of age (27%). In the group that received nitisinone before 30 days of age, no transplantations were needed.

Treatment of nitisinone was also related to lower incidence of HCC; 5% in the NTBC study developed HCC compared with 8% in the historical control. In the NTBC study, all patients diagnosed with HCC were older than one year of age except one. In addition, nitisinone is associated with decreased risk of porphyric crises and fewer hospitalizations related to HT-1 complications. Shortly after the start of nitisinone, urine SA was reduced to below the reference limit (less than 1 mmol/mol creatinine). Nitisinone was associated with increased plasma levels of tyrosine and decreased levels of alpha-fetoprotein and increased platelet count.

Harms

Nitisinone was generally well tolerated. In the NTBC study, eye disorders (conjunctivitis, blepharitis, keratitis, eye pain, photophobia, and corneal opacity with symptoms of itching, burning, photophobia, corneal erosion, and corneal clouding) were the most commonly reported adverse events (AEs), with 31 events observed in 14 patients. In the Quebec study, one patient developed photophobia and corneal crystals, which disappeared within 24 hours of strict dietary restriction. Transient thrombocytopenia, neutropenia, or both were reported in 3%, 3%, and 1.5% of the study population, while there were no infections or bleeding that could be ascribed to the observed neutropenia or thrombocytopenia.

In the NTBC study, 49 serious adverse events (SAEs) were reported, including liver failure, HCC, multi-organ failure, elective liver transplantation, and thrombocytopenia. However, most of these SAEs were considered to be related to the underlying disease, not nitisinone treatment. Three cases of severe thrombocytopenia were deemed to be related to the treatment of nitisinone. No patient has been withdrawn because of AEs of nitisinone in the NTBC study. Ten deaths in the NTBC study and two patients in the Quebec study were reported.

Conclusions

Two manufacturer-submitted single-arm, open-label studies demonstrated an association between treatment with nitisinone in combination of dietary restriction of tyrosine and phenylalanine and improved survival in patients with HT-1 as compared with a historical population that received dietary treatment alone. Greater survival benefits were observed in patients who started treatment before two months of age. Nitisinone was also associated with reduced risk of liver failure, fewer liver transplantation requirements, lower risk of HCC, fewer porphyric crises and reduced acute complications of HT-1. Delayed nitisinone treatment (i.e., after six months of age) was associated with an increased risk of HCC and requirement for liver transplant. Eye disorders related to elevated plasma tyrosine levels with nitisinone treatment were the most commonly reported AEs. Thrombocytopenia and neutropenia may also occur with nitisinone treatment, although no serious sequelae were identified in the studies. Most of the reported SAEs were considered likely related to the underlying disease and not nitisinone.

The included studies were limited by the open-label design and lack of a direct comparator. Moreover, no absolute or relative measures of effect with formal statistical comparisons were performed on the outcomes between nitisinone plus dietary restriction versus dietary restriction alone, and therefore there is uncertainty as to the magnitude of any benefit from nitisinone as compared with dietary restriction. However, the relatively large difference in survival probabilities (primarily if initiated in those younger than six months) and reduced morbidity as compared with a historical control, suggest there is an overall clinically significant beneficial effect with nitisinone in treating patients with HT-1, although the extent to which this would be maintained over a lifetime (approximately 80 years, based on Canadian general population estimates) is associated with uncertainty.

Table 1: Summary of Results

Outcome	The NTBC Study				The Quebec Study		
	Nitisinone Plus Dietary Restriction (N = 207)		Dietary Restriction Alone (Historical Cohort) (N = 108)		Nitisinone-Naive (Historical Cohort) (N = 28)	Late Treatment (N = 26)[a]	Early Treatment (N = 24)[a]
Efficacy							
Survival probability (95% CI)							
	2-year	4-year	2-year	4-year			
Overall	96% (93 to 99)	93% (88 to 98)	NR		20 patients (71.4%) before transplant; 18 (90%) after transplant.	26 patients (100%) before transplant; 5 (72%) after transplant.	24 patients (100%) before transplant; 24 (100%) after transplant.
Start age 0 to 2 months	88% (65 to 100)	88% (52 to 100)	29%	29%	NR		
Start age 0 to 6 months	94% (85 to 100)	94% (80 to 100)	74%[b]	60%[b]			
Start age > 6 months	97% (94 to 100)	93% (85 to 100)	96%	96%			
Survival without liver transplant							
Overall	84% (78 to 90)	78% (69 to 86)	NR		NR		
Start age 0 to 2 months	88% (65 to 100)	88% (52 to 100)					
Start age 0 to 6 months	85% (75 to 95)	82% (66 to 97)					
Start age > 6 months	83% (76 to 91)	76% (65 to 87)					
Liver failure, n (%)							
Death related to liver failure	7 (3.4)		27 (25)		NR	NR	No early-treated patients had developed

Outcome	The NTBC Study		The Quebec Study		
	Nitisinone Plus Dietary Restriction (N = 207)	Dietary Restriction Alone (Historical Cohort) (N = 108)	Nitisinone-Naive (Historical Cohort) (N = 28)	Late Treatment (N = 26)[a]	Early Treatment (N = 24)[a]
					detectable liver disease after more than 5 years of treatment
Liver transplantation, n (%)					
	27 (13)	26 (25)	20 (71)	7 (26.9)	0
HCC, n (%)					
	10 (5)	9 (8)	NR	1 (3.8)	NR
Porphyric crises, n (%)					
	1 (0.5)	10% of the patients died from consequences of porphyria-like crises	Spent 71 months for neurologic crises in hospital	Spent 17 months for neurologic crises in hospital	0
Biochemical variables					
Urine SA	> 90% of all patients normalized by 2 weeks (< 1 mmol/mol creatinine)	NR	Urine SA levels decreased 7.3-fold 12 hours following the first dose of NTBC; after 1 week of nitisinone therapy, urine SA levels were not significantly different from those ≥ 3 months later. Data were presented graphically		
Tyrosine (µmol/L)	140	387	Tyrosine levels increased following nitisinone administration. Data were presented graphically.		
Harms					
SAEs, n (%)	3 (1.4)[c]	NR	NR		
WDAEs, n (%)	0	NR	NR		

CI = confidence interval; HCC = hepatocellular carcinoma; NR = not reported; SA = saccinylacetone; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] "Late-treatment" means nitisinone treatment started after 30 days of age; "early treatment" means nitisinone treatment started before 30 days of age.
[b] Data corresponded to patients two to six months of age at start of treatment.

[c] 49 SAEs were reported, while three of them were considered to be treatment-related.

Sources: European Medicines Agency report,[2] FDA medical review,[3] Larochelle 2012,[4] van Spronsen 1994.[5]

Introduction

Disease Prevalence and Incidence

Hereditary tyrosinemia type-1 (HT-1) is a rare, life-threatening, autosomal recessive disorder of amino acid metabolism. A deficiency of fumarylacetoacetate hydrolase (FAH), which is the last enzyme in the pathway of tyrosine catabolism, results in the accumulation of toxic metabolites (succinylacetone [SA] and succinylacetoacetate [SAA]) in the FAH-deficient hepatocytes and proximal renal tubular cells, and subsequently leads to liver and kidney damage.[6] HT-1 typically manifests in infancy and is characterized by elevated plasma tyrosine levels.[6] Liver dysfunction, such as bleeding abnormalities, hypoglycemia, ascites, edema, vomiting, irritability, and jaundice, is the dominant clinical manifestation in children who are not detected by the newborn screening. Progression of the liver disease can be chronic or acute, with rapid deterioration.[6-8] Other clinical manifestations of HT-1 include renal tubular dysfunction, hypophosphatemic rickets, porphyria-like neurological crises, hypoglycemia due to islet cell hyperplasia, and cardiomyopathy. The lifetime risk of patients with HT-1 developing hepatocellular carcinoma (HCC) is high (37% in the survivors without treatment).[6,9,10] Furthermore, many patients suffer from neurocognitive deficits, which may be attributed to tyrosine toxicity, phenylalanine deficiency, drug toxicity, or natural disease progression in long-term survivors.[11] If untreated, survival in patients with HT-1 is less than 12 months of life. Most of these children die as a result of liver failure and severe coagulopathy.[12,13]

The prevalence of HT-1 ranges from one in 12,000 to one in 100,000 individuals of Northern European descent.[6] In Canada, the estimated prevalence was one in 17,609 individuals,[14] although a remarkably higher prevalence (one in 1,846 live births) was observed in the Saguenay–Lac-Saint-Jean region in Quebec, and the estimated carrier rate of a specific mutation was one in 20 to 25 inhabitants.[6,13]

Newborn screening allows for earlier identification of the disorder and earlier intervention.[15] Previous research suggests better outcomes when treatment begins at an asymptomatic stage.[15] The accuracy of the newborn screening test using tandem mass spectrometry measurement of SA from dried blood spots is as high as 100%.[15] Detection of SA in urine, plasma, or amniotic fluid is considered pathognomonic of tyrosinemia, as SA is not found in any other condition. Province-wide newborn screening for tyrosinemia has been practised since 1970 in Quebec,[16] and the presence of SA in urine or blood is used as a confirmatory test in the Quebec newborn screening program.[12] Compared with other regions, children in Quebec were identified and treated from an early stage of the disease due to the universal neonatal screening.[16] All other Canadian provinces and territories, except for New Brunswick, Nova Scotia, and Prince Edward Island, have included screening for HT-1 through their newborn screening programs since 2015.[17]

Standards of Therapy

Before the introduction of nitisinone, the management of HT-1 involved dietary restriction of phenylalanine and tyrosine and supportive treatment, until liver transplantation if possible.[9] Despite a strict dietary regimen started within days of birth, progression of cirrhosis or HCC, as well as inconsistent improvement in renal tubular function, were still observed.[12,16]

At present, all affected children are managed with nitisinone in combination with a tyrosine- and phenylalanine-restricted diet.

Liver transplantation remains the only definitive therapy for patients with HT-1, when the patients do not respond to nitisinone therapy and there is progressive liver failure, or they have suspected HCC.[9,15] However, liver transplantation is associated with risks of operative complications, including death, graft rejection, and the challenge of organ availability.[18]

In Quebec, provision of services to all patients is coordinated by the four university hospital centres and by a regional centre in the area with the highest prevalence of HT-1. Because of the universal neonatal screening for tyrosinemia, HT-1 patients are usually first identified as clinically asymptomatic newborns in Quebec.[16] Information as to coordination of care in other provinces and territories was not available for this review. Screen-positive babies are usually seen within three weeks of birth, and the follow-up examinations, such as physical exams, liver function, coagulation tests, and SA levels, are conducted. Patients who have positive screen results but normal liver function are not treated but are followed closely while awaiting the results of specific tests. When evidence of liver dysfunction is observed, nitisinone and a special diet are offered to the patients. Plasma nitisinone levels are used to adjust the prescription of nitisinone.[7,16]

Drug

Nitisinone (Orfadin) is a competitive inhibitor of 4-hydrooxyphenylpyruvate dioxygenase, an enzyme upstream of FAH in the tyrosine catabolic pathway. By inhibiting the normal catabolism of tyrosine in patients with HT-1, nitisinone prevents the accumulation of the catabolic intermediates, which can be converted to the toxic metabolites SA and SAA, which are responsible for liver and kidney damage.[19] The effect of nitisinone on inhibiting catabolism of tyrosine also leads to an increase in plasma tyrosine levels. Therefore, treatment with nitisinone requires restriction of the dietary intake of tyrosine and phenylalanine to prevent tyrosine toxicity, such as ocular symptoms, intellectual disability, developmental delay, or painful hyperkeratotic plaques on the soles and palms. Plasma tyrosine levels should be maintained below 500 µmol/L to decrease the risk of ocular disorders.[19,20]

Nitisinone is supplied as capsules containing 2 mg, 5 mg, 10 mg, or 20 mg of nitisinone. An oral suspension formulation (4 mg/mL) was approved during the course of the CADTH Common Drug Review (CDR). However, this formulation is not assessed in the current review. Nitisinone was provided to Canadian patients beginning in 1994 by Swedish Orphan Biovitrum AB (Sobi), under the Health Canada Special Access Programme, which ended in late 2016.[21] A Notice of Compliance for nitisinone for the treatment of adult and pediatric patients with HT-1 in combination with dietary restriction of tyrosine and phenylalanine was granted by Health Canada on December 13, 2016.[1] The recommended initial dosage of nitisinone is 1 mg/kg body weight per day, in two divided doses orally. The dose of nitisinone should be adjusted individually based on weight, biochemical, and enzyme markers. The maximum daily dose of nitisinone is 2 mg/kg.[19] Two other nitisinone products have received Health Canada approval for the treatment of HT-1: MDK-nitisinone (manufactured by Mendelikabs Inc.) and nitisinone tablets (manufactured by Cycle Pharmaceuticals Ltd.).[22] However, these have not been reviewed by CDR as of writing of this review.

Objectives and Methods

Objectives

To perform a systematic review of the beneficial and harmful effects of nitisinone (capsules 2 mg, 5 mg, 10 mg, and 20 mg) for the treatment of patients with HT-1 in combination with dietary restriction of tyrosine and phenylalanine.

Methods

All manufacturer-provided trials considered pivotal by Health Canada were included in the systematic review. Phase III studies were selected for inclusion based on the selection criteria presented in Table 2.

Table 2: Inclusion Criteria for the Systematic Review

Patient Population	Patients with HT-1 in combination with dietary restriction of tyrosine and phenylalanine
Intervention	Nitisinone
Comparators	Best supportive care (dietary restriction of tyrosine and phenylalanine)
Outcomes	**Key efficacy outcomes:** Survival Liver failure Liver transplantation Renal failure HCC HRQoL measured with validated scales **Other efficacy outcomes:** Porphyric crisis Biochemical variables • HT-1–related: SA, tyrosine, etc. • Hepatic: PT/PTT, INR, hepatic transaminase, AFP, etc. • Renal: creatinine, GFR, etc. • Hematologic: erythrocyte count, thrombocyte count, neutrophil count, etc. Hospitalization resulting from acute complications of HT-1 **Harms outcomes:** AEs, SAEs, WDAEs, mortality, notable harms/harms of special interest (ocular AEs, hematological symptoms, cutaneous symptoms, tyrosine levels, etc.)
Study Design	Published and unpublished phase III RCTs

AFP = alpha-fetoprotein; AE = adverse event; GFR = glomerular filtration rate; HCC = hepatocellular carcinoma; HRQoL = health-related quality of life; HT-1 = hereditary tyrosinemia type 1; INR = international normalized ratio; PT = prothrombin time; PTT = partial thromboplastin time; RCT = randomized controlled trial; SA = succinylacetone; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

The literature search was performed by an information specialist using a peer-reviewed search strategy.

Published literature was identified by searching the following bibliographic databases: Ovid MEDLINE(R) Epub Ahead of Print, In-Process and Other Non-Indexed Citations; Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present; Embase (1974–) via Ovid; and PubMed. The search strategy consisted of both controlled vocabulary, such as the National

Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concept was the drug name (Orfadin – nitisinone).

No methodological filters were applied to limit retrieval. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year or by language. Conference abstracts were excluded from the search results. See Appendix 2 for the detailed search strategies.

The initial search was completed on September 26, 2017. Regular alerts were established to update the search until the meeting of the CADTH Canadian Drug Expert Committee on January 17, 2018. Regular search updates were performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) was identified by searching relevant websites from the following sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters):

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Google and other Internet search engines were used to search for additional Web-based materials. These searches were supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts. In addition, the manufacturer of the drug was contacted for information regarding unpublished studies.

Two CDR clinical reviewers independently selected studies for inclusion in the review based on titles and abstracts, according to the predetermined protocol. Full-text articles of all citations considered potentially relevant by at least one reviewer were acquired. Reviewers independently made the final selection of studies to be included in the review, and differences were resolved through discussion. Included studies are presented in Table 3.

Results

Findings from the Literature

No studies were identified from the literature for inclusion in the systematic review (Figure 1). Two studies submitted by the manufacturer are included. The included studies are summarized in Table 3 and described in “Included Studies.”

Figure 1: Flow Diagram for Inclusion and Exclusion of Studies

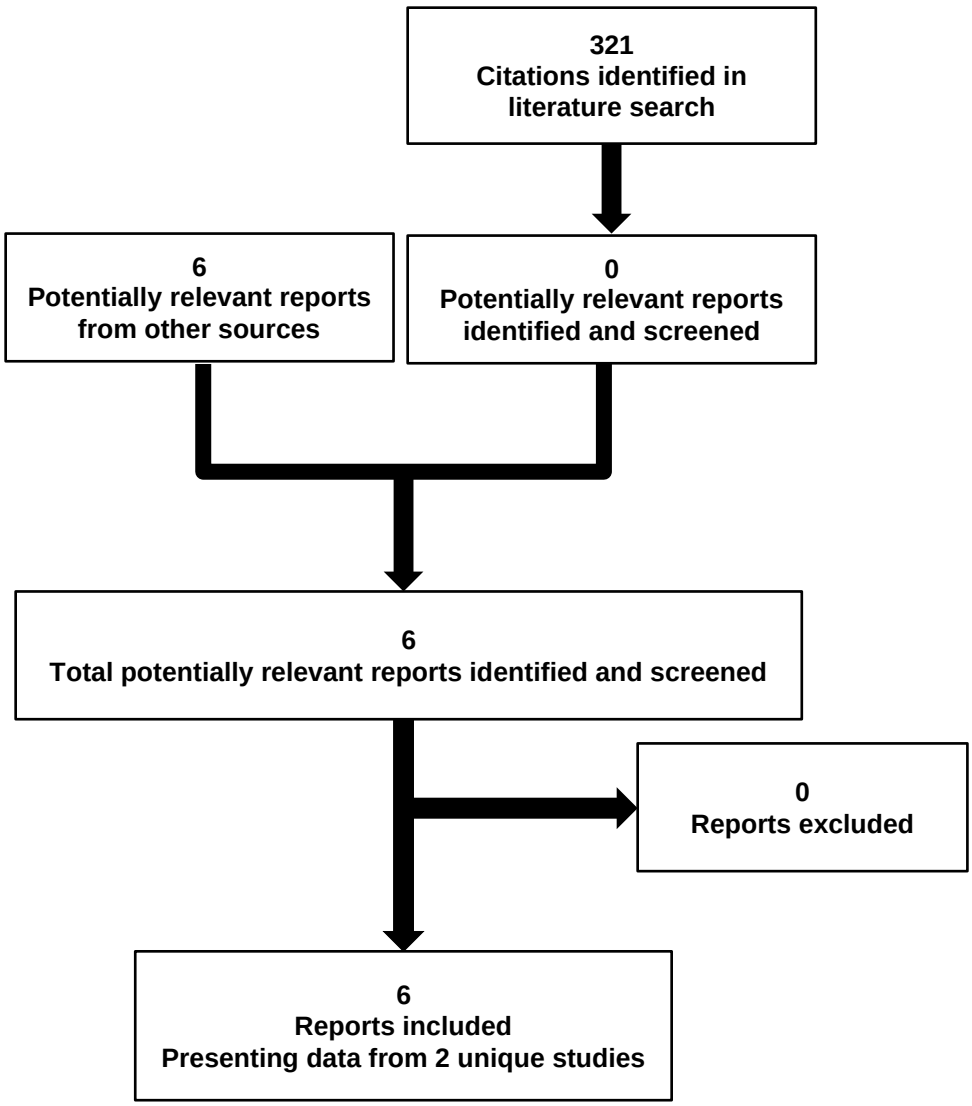

Table 3: Details of Included Studies

		The NTBC Study	The Quebec Study
Designs & Populations	**Study Design**	Phase II-III, single-arm, open-label, multi-centre trial	Single-arm, open-label trial
	Locations	25 countries including Canada and the US	Quebec, Canada
	Enrolled (N)	207 patients enrolled between February 1991 and August 1997 for the main analysis 250 patients enrolled between July 1993 and March 2000 for the complementary analysis	78 patients born between February 1984 and February 2004
	Inclusion Criteria	HT-1 verified by the presence of SA in the urine or plasma	All known HT-1 patients in Quebec born between February 1984 and February 2004
	Exclusion Criteria	Prior liver transplantation	Not specified in the published article
Drugs	**Intervention**	Nitisinone	Nitisinone late-treatment Nitisinone early treatment
	Comparator(s)	Historical control, where patients received dietary treatment only.	Nitisinone-naive patients enrolled before 1994; patients received dietary treatment and other supportive therapy
Duration	**Phase**		
	Run-in	N/A	
	Double-blind		
	Follow-up	Patients were enrolled on an ongoing basis; all patients entered up to the point of data cut-off on August 21, 1997 were included in the main analysis	Data for events before 1994 were obtained from retrospective chart review, while subsequent data were recorded prospectively until liver transplant, death, or date of data analysis (August 1, 2009)
Outcomes	**Primary End Point**	Survival Survival without need for liver transplantation Death due to liver failure HCC Porphyric crises	Hospitalization due to acute complications of HT-1 Survival Liver transplantation Neurological crises
	Other End Points	Biochemical variables of liver function, kidney function, hemic system, SA, and tyrosine	Biochemical variables of liver function, kidney function, hemic system, SA, and tyrosine
Notes	**Publications**	Holme 1998[23] Holme 2000[24]	Larochelle et al. 2012[4]

HCC = hepatocellular carcinoma; HT-1 = hereditary tyrosinemia type 1; N/A = not applicable; SA = saccinylacetone.

Note: Three additional reports were included (FDA Medical Review,[3] Australian public assessment report[25] and European Medicines Agency report[2]).

Source: Holme 1998,[23] Holme 2000,[24] and Larochelle 2012.[4]

Included Studies

Description of Studies

The NTBC study was a single-arm, open-label, multinational study to investigate the efficacy and safety of nitisinone in combination with a restricted diet. The study was coordinated at Sahlgrenska University Hospital, Gothenburg, Sweden, and conducted over nine years. It included a main analysis of 207 patients who were recruited between February 1991 and August 1997, and a complementary analysis of 250 patients who were recruited between July 1993 and March 2000. Any patients with a diagnosis of HT-1, except

for those with prior liver transplantation, were eligible for inclusion. Eligible participants received oral nitisinone therapy with concomitant dietary restriction of tyrosine and phenylalanine. The study protocol required that laboratory and clinical data be reported to a common database in Gothenburg, and that urine and blood samples be sent there for measurement of critical variables. For ethical reasons the study was open-label and comparisons were made with a historical control (108 patients treated with a diet restricted in tyrosine and phenylalanine alone; the time period over which patients were recruited for the historical cohort was not specified[5]).[3]

The NTBC study was not performed according to the current Good Clinical Practice rules, and was sponsored by industry and non-industry funding.

The Quebec study was a single-arm, open-label study conducted in Quebec, Canada. All known HT-1 patients born between February 1984 and February 2004 were included in this study. The outcomes of children born during the first 10 years that nitisinone became available in Quebec were compared with those of patients born in the preceding decade, during which all current treatment options except nitisinone were available, including newborn screening, diet therapy, and liver transplantation. The clinical course of patients was recorded until liver transplantation, death, or August 1, 2009 (date of data analysis), whichever came first. Data for events before 1994, when nitisinone was unavailable to the Canadian patients, were obtained from retrospective chart review, while subsequent data were recorded prospectively.

The Quebec study was supported by non-industry funding.

Populations

Inclusion Criteria

All patients who were diagnosed with HT-1, regardless of age of symptom presentation and treatment experience, were included in the two studies. The diagnosis of HT-1 was confirmed by the presence of elevated levels of SA in blood or urine.

In the Quebec study, three patient groups were examined: nitisinone-naive, late treatment (nitisinone started after 30 days of age), and early treatment (nitisinone started on or before 30 days of age). In the two nitisinone-experienced groups, eligible participants were required to have received nitisinone for at least two weeks and lack documented nonadherence (which was defined as patient confirmation that they did not adhere to the nitisinone regimen and had documented, inappropriately low, plasma nitisinone levels).

Exclusion Criteria

In the NTBC study, patients with prior liver transplantation were excluded from the studies.

In the Quebec study, all known HT-1 patients in Quebec born between February 1984 and February 2004 were eligible. Exclusion criteria were not specified in the published articles for the Quebec study.

Baseline Characteristics

In the NTBC study, 207 patients were included between February 1991 and August 1997 for the main analysis and 250 patients were included between July 1993 and March 2000 for the complementary analysis. Thirty-nine Canadian patients in this study were also included in the Quebec study.

The median age of patients at enrolment was nine months with a range of 0 to 21.7 months.[3] After 1993, more patients younger than one year of age were enrolled compared with earlier years of the study.[23] In more recent years, about 66% of the study participants were diagnosed before six months of age and more than 80% were diagnosed before two years of age.[24] The age at start of treatment ranged from the first day of life to 21 years. However, this wide spectrum was most apparent during the first years of the study, and the number of patients with onset of nitisinone treatment before one year of age had increased over the years. There were more boys (n = 114) than girls (n = 93) included in the study.

In the Quebec study, 78 patients were enrolled: 28 never received nitisinone, 26 were in the late-treatment group and 24 were in the early-treatment group. Demographic characteristics of these study participants were not reported.

Details of the patient characteristics are presented in Table 4.

Table 4: Summary of Baseline Characteristics

	The NTBC Study	The Quebec Study
Total, N	207	78
Male, n (%)	114 (55)	NR
Female, n (%)	93 (45)	
Age at enrolment (median, range)	9 months (0 to 21.7 years)	
Age 0 to 2 months at start of treatment, n (%)	16 (7.7)	
Age 0 to 6 months at start of treatment, n (%)	80 (39)	
Age 6 to 24 months at start of treatment, n (%)	62 (30)	
Age > 24 months at start of treatment, n (%)	65 (31)	

NR = not reported.

Source: FDA medical review,[3] European Medicines Agency report.[2]

Interventions

In the NTBC study,[23,24] nitisinone was administered orally twice daily, initially at a daily dose of 0.6 mg/kg bodyweight. Individual dosage readjustments were based on the biochemical response as estimated by measurements of serum and urine SA, and other biochemical markers. From 1994, 1 mg/kg was recommended as total daily initiation dose. For some patients (especially infants) an increased dose up to 2 mg/kg may be required. No patients received more than 3 mg/kg/day. It was recommended that the plasma tyrosine level be kept below 500 µmol/L to avoid adverse effects resulting from the nitisinone therapy.

From the beginning of the study, nitisinone was distributed from the Sahlgrenska University Hospital in Gothenburg, Sweden, to hospitals all over the world on a compassionate use basis. From late 1994 the distribution of nitisinone was gradually shifted from the hospital to Sobi, the manufacturer of Orfadin. After 1996, Sobi was responsible for providing the drug.

In the Quebec study, 4 dosages of nitisinone were initially fixed at 0.6 or 1 mg/kg/day in two daily oral doses. For the first two years of the study, patients received a recrystallized preparation of nitisinone supplied by Lindstedt and Holme. Thereafter, they received commercially produced nitisinone. After 1999, nitisinone doses were titrated to minimize urine SA levels. The maximum daily dose of nitisinone was 2 mg/kg.[16] Dose adjustment was based on plasma nitisinone level.[16] The plasma tyrosine level was kept between 200 µmol/L and 400 µmol/L to avoid the nitisinone-related adverse effects in this study.

In both studies, the study drug was provided as an adjunct to dietary restriction of tyrosine and phenylalanine in the treatment of HT-1. No information on other drugs and/or supportive care was allowed in the studies.

Outcomes

Survival

In the NTBC study, survival was measured as overall survival, survival time without need for liver transplantation, and death due to liver failure during treatment with nitisinone. In the Quebec study, survival data were reported as death before and after transplantation. This was one of the primary outcomes in the NTBC study.

Liver Failure

Liver failure was not specifically defined in the included studies, although presence of jaundice, elevated (not defined) aminotransferase levels, and abnormal coagulopathy were considered signs of liver failure. This outcome was presented as “death due to liver failure” and “transplantation due to liver failure” during the treatment with nitisinone in the included studies. This was one of the primary outcomes in the NTBC study.

Renal Failure

Renal failure was not defined in the included studies, although hypophosphatemia and greatly elevated alkaline phosphatase levels were considered signs of renal failure.

Liver Transplantation

In the included studies, liver transplantation was performed on patients who did not respond well to the nitisinone treatment (not defined), or those with progressive liver disease and suspected HCC. This was one of the primary outcomes in the NTBC study.

HCC

The measurement of HCC included death due to cancer, transplantation due to cancer, or cancer diagnosed during treatment with nitisinone. This was one of the primary outcomes in the NTBC study.

Porphyric Crisis

“Porphyric crisis” was measured in the NTBC study, while “neurological crisis” was reported in the Quebec study. This outcome was not defined in the included studies. Neurologic crisis was defined as “painful episodes affecting extremity and/or abdominal function, accompanied by hypertension and hyponatremia” in the literature,[10] and is considered interchangeable with porphyric crisis. This was one of the primary outcomes in the NTBC study.

Biochemical Variable

HT-1–related biochemical parameters (e.g., plasma and urine SA and plasma tyrosine), liver function (e.g., serum alanine transaminase [ALT], aspartate transaminase [AST] prothrombin complex and serum alpha-fetoprotein), renal function (e.g., serum creatinine), and hemic system (e.g., complete blood count) were recorded in both studies. In the NTBC study, site physicians sent patients’ blood and urine samples collected before nitisinone treatment and at regular intervals during the treatment to be analyzed at the Sahlgrenska

Hospital laboratory. The Quebec study did not explicitly state where blood and urine samples were evaluated.

Urinary SA level is a sensitive marker for the efficacy of nitisinone treatment in patients with inherently high levels of SA production. A reduction to below the detection limit means a thousand-fold reduction of the flux through the tyrosine catabolic pathway. However, in patients with barely detectable SA before start of treatment with nitisinone, disappearance of SA is no guarantee of effective treatment. There is a good correlation between urine SA level and the plasma SA level. See Appendix 4 for more details about urinary and plasma SA analysis.

Hospitalization Due to Acute Complications of HT-1

This included hospitalizations for preventive treatment and observation during infections, and was a primary outcome in the Quebec study.

Safety

Adverse events (AEs), serious AEs (SAEs), withdrawal due to AEs (WDAEs), and mortality were reported in the included studies.

Statistical Analysis

The NTBC study was an investigator-initiated study designed to include all patients with verified HT-1 who were willing to participate and who did not have a history of a previous liver transplant, with the primary objective of providing patients with compassionate access to nitisinone. No sample size or power calculations and no formal statistical analysis plan were reported.

Over the period from February 1991 to August 1997, the study cumulatively enrolled 207 patients. All were included in the main data analysis. The Kaplan–Meier analysis was used to evaluate survival, occurrences of liver transplantation, liver failure leading to death or liver transplantation, HCC, and porphyric crisis. No adjustments were made in the analyses for variation due to country and/or centre. All statistical tests were two-sided and no formal adjustments for multiple testing were made. The Wilcoxon signed rank test was used to compare differences in numerous outcomes pre-treatment and post-treatment (e.g., one year after initiation of nitisinone), and comparisons were within group only. A formal statistical comparison between the nitisinone-treated patient populations and the historical control was not conducted. Data from patients withdrawing from the study were used up to the point of withdrawal. Missing data were not imputed except in the analyses of nitisinone dose and in the description of the extent of exposure where the last reported dose was carried forward.[25]

In addition to the main analysis regarding the 207 patients who were included between February 23, 1991, and August 21, 1997, (and who received a relatively lower initial dose of 0.6 to 1 mg/kg), a complementary analysis was conducted on the 250 patients who were included between July 1, 1993, and March 28, 2000, after all investigators had received the recommendations of an initial daily dose of 1 mg/kg body weight.[2] The purpose of the complementary analysis was to update the main analysis with an evaluation of patients who received the recommended initial daily dose of 1 mg/kg.

In the Quebec study, data for events before 1994 were retrospectively collected, while the subsequent data were prospectively recorded. For the outcome of “hospitalizations related to the acute complications of HT-1,” each month was classified as to whether the patient

had received nitisinone during that month, and whether an acute event (e.g., neurological crisis or hospitalization for HT-1–related reasons other than a neurological crisis) occurred during the month. Treatment groups were compared using the chi-square test. The course of each patient was divided into calendar months.

Analysis Populations

The NTBC Study

In the main analysis of the NTBC study, all patients who started treatment from February 23, 1991, until August 27, 1997, were included in the survival analyses and patients were censored after August 27, 1997. In the complementary NTBC analysis, all patients who started treatment from July 1, 1993, to March 28, 2000, were included in the survival analyses and patients were censored at March 28, 2000. In both the main and complementary NTBC analyses, assessments of outcomes were undertaken in the overall population and in subgroups based on age at the start of nitisinone treatment.[25] The safety evaluation was mainly based on a total of 207 patients and 441 patient-years.[2]

Historical Control

In an international survey, 108 patients from 15 countries who had been diagnosed with HT-1 and were treated with a tyrosine- and phenylalanine-restricted diet filled out a standardized questionnaire.[5] Among them, 83 patients (77%) had the acute, 15 the subacute, and 10 the chronic form of disease. The diagnosis was confirmed in patients with characteristic clinical features in combination with increased urinary SA or decreased activity of fumarylacetoacetase and also in patients with characteristic clinical features who had a sibling with proven HT-1. This cohort was used as historical control in the NTBC study.

The Quebec Study

In the Quebec study, three patient groups were examined, including nitisinone-treatment–naive, late-treatment and early-treatment groups. The nitisinone-treatment–naive group was used as the historical cohort.

Patient Disposition

At the time of data cut-off, 38 of the 207 patients withdrew from the NTBC study. The main reasons for the withdrawals were death and liver transplantation (Table 5).

In the Quebec study, patient withdrawal was not specifically reported. Ten patients never treated with nitisinone died (eight before liver transplantation and two after liver transplantation). By comparison, two deaths were reported among the patients who received nitisinone treatment after 30 days of age. Twenty nitisinone-naive patients and seven patients who received nitisinone after 30 days of age underwent liver transplantation, respectively.

Table 5: Patient Disposition

	The NTBC Study	The Quebec Study	
Enrolled, N	N = 207	N = 78	
	nitisinone	nitisinone-treated (n = 50)	nitisinone-naive (n = 28)
Discontinued, n (%)	38 (18)	39 (50)[a]	
Death during nitisinone treatment	10	0 died before liver transplant, 2 in the late-treatment group died after transplant	10 in total: 8 died before liver transplant, 2 died after transplant.
Liver failure	7 (7 died)		
HCC	2 (2 died)		
Multi-organ failure	1 (1 died)		
Liver transplantation	27	7 (late-treatment group)	20 (71)
Elective	7 (3 died)		Cirrhosis or cancer 13, acute liver failure 2, neurological crises 5
Liver failure	7 (0 died)		
Suspected HCC, verified	7 (2 died)		
Suspected HCC, not verified	6 (0 died)		
Patients' wish to discontinue	1 (1 died)	NR	NR

HCC = hepatocellular carcinoma; NR = not reported.

[a] Calculated by CADTH Common Drug Review.

Source: European Medicines Agency report,[2] Larochelle 2012.[4]

Exposure to Study Treatments

In the NTBC study, the median duration of treatment was 22.2 months with a minimum of 0.1 months and a maximum of 77.9 months. The total exposure in the NTBC study includes more than 1,300 patient-years.[2] Of all patients enrolled in the NTBC study, 83% remain on nitisinone treatment. The usual daily dose before mid-1993 was about 0.6 mg/kg and after that time it was usually about 1 mg/kg. In the main analysis, most patients were treated with a daily nitisinone dose of 0.8 mg/kg to 1.2 mg/kg.[25] In the complementary analysis, the total treatment period ranged from 0.1 months to 80.5 months.[25]

Of the 78 patients participating in the Quebec study, 28 never received nitisinone, 26 were treated after 30 days of age and 24 were treated before 30 days of age. A total of 1,312 patient-months without nitisinone treatment and 5,731 with nitisinone treatment were recorded.

Critical Appraisal

Internal Validity

The NTBC study and the Quebec study were single-arm, open-label studies evaluating the efficacy and safety of nitisinone in patients with a rare disease, HT-1. Patients in both studies were not randomized to a comparator arm, but rather compared with a historical control. These study characteristics are the main limitations of both studies. HT-1 is an uncommon disease that, prior to nitisinone, did not have another drug treatment. A study in an initial group of five Swedish HT-1 children treated with nitisinone (oral daily dose of 0.1 to 0.6 mg/kg) over approximately eight months reported marked reductions in baseline plasma SA concentrations as well as concentrations of other toxic metabolites in the tyrosine metabolic pathway, and improved liver function.[26] Based on these results, it was concluded that it would be unethical to include a placebo group in subsequent studies, and the NTBC study was therefore open-label and did not have a control group. Following

consultation with a clinical expert involved in the review, and based on the natural history of HT-1, experience using nitisinone via Health Canada's Special Access Programme, and the lack of a viable comparator, use of an historical control group on which to base comparisons in this case was deemed reasonable. A patient population participating in an international survey conducted by van Spronsen et al. was used as a historical control for the NTBC study.[5] This study was published in 1994, although the time period during which the participants were enrolled was unclear. In this study, a diagnosis of HT-1 was established with characteristic clinical features in addition to abnormal levels of metabolites or a sibling's proven diagnosis of HT-1. Patients who were identified by neonatal screening were excluded because dietary treatment was started before clinical symptoms had developed. Although age distribution of the study participants was not reported, it suggests that these patients experience a delay between the first presenting symptom and the time of diagnosis, and they were more likely to have more severe disease, compared with those in the NTBC study. There were significant clinical heterogeneities between the nitisinone-treated patient population and the historical population, and part of the survival benefits in the NTBC study could be attributed to early identification of the disease and early intervention. Information regarding the onset of symptoms, the time of diagnosis, the performance of liver transplantation, the survival, the suspicion of possible development of tumour, and existence of proven HCC and the cause of death was collected. The Kaplan–Meier method was used for the estimation of survival probabilities. It is unknown if propensity scores were used to help minimize differences between cohorts in comparison between the two populations. No other adjustments were performed to eliminate the impact of potential confounders and/or effect modifiers.

The diagnosis of HT-1 was confirmed by measuring urine or blood SA when a positive newborn screening result was found. As this method is recommended by published literature and clinical practitioners,[10] a misdiagnosis was unlikely in the study population. Furthermore, the study protocol required that laboratory and clinical data be reported to a common database in Gothenburg, Sweden, and that urine and blood samples be sent there for measurement of critical variables. As a result, the risk of potential review bias was likely reduced.

There was a change in the study drug formulation during the NTBC study, from a lactose formulation to pregelatinized starch formulation. The bioequivalence between the two formulations has been demonstrated in healthy adult volunteers and patients with HT-1[2,25] and therefore this change is unlikely to affect the validity of the results in a meaningful way. Also, the initial dosage of nitisinone increased from 0.6 mg/kg/day during the first years of the study to 1 mg/kg/day after 1993 because the investigators did not think the original dosage was sufficiently effective due to persistence of high levels of metabolites. The 207 patients enrolled between February 1991 and August 1997 in the main analysis received the lower doses and 250 patients enrolled between July 1993 and March 2000 received the currently recommended dose of 1 mg/kg. The maximum daily dose was 3 mg/kg. It is estimated that the analyses shared about 150 patients enrolled in a common overlapping time period.[25] As a result of the substantial number of shared patients, the results of the two analyses tended to be similar. On the other hand, compared with the lower dose, the dose of 1 mg/kg may result in more clinical benefits, as well as more drug-related adverse effects.

Formal statistical comparisons were complicated by the essentially observational nature of the included studies and use of a historical control. Because of the variation in study design, there were significant heterogeneities between the cohorts, for instance the

inclusion criteria of the included studies, age of onset of symptoms, previous treatment, and change in practice pattern such as improved newborn screening and earlier intervention. These are potential confounders for study drug evaluation, but the data analyses did not adjust for them. Subgroup analyses would be challenging in studies with a small sample size. It is unclear how this would affect the comparisons between the study participants in the NTBC study and the historical population.

In the NTBC study, patients were enrolled on an ongoing basis and all patients entered up to the point of data cut-off on August 21, 1997, have been included in the main analysis. Therefore, as expected with this type of cohort, each patient had been on treatment for a different period of time, and the number of patients who were available for inclusion in survival analysis after two and four years of treatment was 95 and 35, respectively. In the absence a statistical power analysis there is uncertainty about how robust the comparisons between cohorts are. This is somewhat mitigated by the large differences in the survival probabilities between the nitisinone-treated cohort and the non-treated historical cohort. Nevertheless, the lack of precise estimates of treatment effects of nitisinone plus dietary restriction relative to dietary restriction alone are important limitations that lead to uncertainty in the data.

The incomplete reporting of results in the Quebec study (lack of description on demographic characteristics and no details reported for some of the biochemical parameters) also limits the ability to interpret the clinical significance of the efficacy results.

External Validity

The studies attempted to include any patient with confirmed HT-1, irrespective of age and clinical condition. The only exclusion criterion in the NTBC study was previous liver transplantation; no exclusion criteria were specified for the Quebec study. Although both studies provided limited descriptions of patient characteristics, discussion with the clinical expert involved in the review suggested that the populations were likely representative of the population in Canada. For patients started on nitisinone after six months of age, and/or with asymptomatic disease, the treatment benefit remains unclear or highly uncertain. Given a precise estimate of treatment effect was unavailable, it is difficult to assess the external validity of the findings.

In addition, the Quebec study would be valuable in assessing the drug in a Canadian context.

Some of the important clinical outcomes identified by the patient groups were not measured, such as health-related quality of life of the patients or caregivers, developmental delay, and cognitive deficits.

Nitisinone should be administered along with a low-tyrosine/phenylalanine diet to patients with HT-1. There is little research regarding adherence to medication or diet in HT-1. However, previous study indicates that adherence may be suboptimal, particularly with regard to dietary restrictions.[27] Patient adherence to recommended treatment regimens was not reported in the included studies, making it impossible to explore the relationship between adherence and treatment effect on death, liver failure, development of HCC and other clinically important outcomes.

Efficacy

Only those efficacy outcomes identified in the review protocol are reported below (Table 2).

Survival

Overall Survival

Higher survival probability was observed in nitisinone-treated patients in the NTBC study compared with those who received dietary restriction only in the historical control, where liver failure and recurrent bleeding were the primary causes of death in this population prior to the introduction of nitisinone, and survival did not extend past 12 years of age for any patients (Table 6).[5]

The two-year and four-year overall probabilities of survival for patients who initiated nitisinone at any age were 96% (N = 95) and 93% (N = 35), respectively. In addition, survival probability was explored in subgroups based on the age of starting nitisinone treatment. For patients who started before two months of age, their two-year and four-year overall survival rates were 88% and 88%, respectively. For those who started before six months of age, the two-year and four-year overall survival rates were 94% and 94%, respectively. For those who started after six months of age, the two-year and four-year overall survival rates were 97% and 93%, respectively. It is unclear whether the initiation of nitisinone therapy was indicated by the occurrence of any symptoms in the NTBC study. In the historical population, the two-year survival rates were 29%, 74% and 96% for patients in whom symptoms developed before two months, from two to six months, and after six months of age, respectively. The four-year survival rates were similar to the two-year survival rate in the historical population for all three subgroups of patients.[3] Results of the complementary analysis were similar to those in the main analysis: the overall survival rate for patients who initiated nitisinone at any age was 93% at two years, four years, and six years (Appendix 3).

In the Quebec study, 10 patients in the treatment-naive group died (eight before liver transplantation and two after liver transplantation; *P* value for between-group difference < 0.01). Two patients in the late-treatment group died, both after liver transplantation (between-group difference was not statistically significant; *P* value not reported).

Survival Without Liver Transplantation

In the NTBC study, the two-year and four-year survival probabilities in patients who did not have liver transplantations were 84% and 78%, respectively.

Liver Failure–Related Death

In the NTBC study, the four-year cumulative probability of death or transplantation due to liver failure was 13%.[3] In the historical population, approximately 32% of the patients died due to liver failure or recurrent bleeding, or were transplanted due to liver failure.[3,5]

Results of survival probability from the complementary analysis in which 250 participants were included are presented in
Appendix 4.

Table 6: Survival Probability

	The NTBC Study				The Quebec Study		
	Patients Treated With Nitisinone + Dietary Restriction[a]		Dietary Restriction Alone (Historical Control)[b]		Nitisinone-Naive (Historical Control)	Late Treatment	Early Treatment
Study Population	**207**		**108**		**78: Nitisinone-naive 28 Late treatment 26 Early treatment 24**		
Survival (95% CI)							
	2 year	4 year	2 year	4 year			
Overall	96% (93 to 99)	93% (88 to 98)	NR		20 patients (71.4%) before transplant; 18 patients (90%) after transplant	26 patients (100%) before transplant; 5 pats (72%) after transplant	24 patients (100%) before transplant; 24 patients (100%) after transplant
Start age 0 to 2 months	88% (65 to-100)	88% (52 to 100)	29%	29%	NR		
Start age 0 to 6 months	94% (85 to 100)	94% (80 to 100)	74%[c]	60%[c]			
Start age > 6 months	97% (94 to 100)	93% (85 to 100)	96%	96%			
Survival without liver transplant							
Overall	84% (78 to 90)	78% (69 to 86)	NR		NR		
Start age 0-2 months	88% (65 to 100)	88% (52 to 100)					
Start age 0-6 months	85% (75 to 95)	82% (66 to 97)					
Start age > 6 months	83% (76 to 91)	76% (65 to 87)					

CI = confidence interval; NR = not reported.

[a] Survival probability of nitisinone + dietary restriction was estimated from the start of nitisinone treatment.

[b] Survival probability of dietary restriction alone was estimated from the onset of symptoms.

[c] Data corresponded to patients 2 to 6 months of age at start of treatment.

Sources: European Medicines Agency report,[2] FDA medical review,[3] van Spronsen et al. (1994).[5]

Liver Failure

In the NTBC study, seven patients of 207 (3.4%) died of liver failure and seven transplantations (3.4%) were performed due to liver failure. In total, 14 patients (6.8%) died or were transplanted due to liver failure in the main analysis (Table 7). For patients whose treatment started before six months of age, seven of 80 (9%) died of liver failure or were transplanted due to liver failure.[2] In the historical control, 25% of patients died of liver failure and transplantation due to liver failure was performed in six of 108 (6.4%) patients. For patients with symptom onset before six months, 35 of 83 (42%) died of liver failure or recurrent bleeding with or without liver failure (data were only reported with recurrent bleeding).[2]

In the Quebec study, no early-treated patients had developed detectable liver disease after more than five years of treatment.

Table 7: Liver Failure (n, %)

	The NTBC Study		The Quebec Study		
Study Population	**Nitisinone + Dietary Restriction**	**Dietary Restriction Alone (Historical Control)[a]**	**Nitisinone-Naive Historical (Control)**	**Late Treatment**	**Early Treatment**
	207	108	28	26	24
Death due to liver failure	7 (3.4)	27 (25)	NR	NR	No patients had developed detectable liver disease after > 5 years of treatment
Transplant for liver failure	7 (3.4)	7 (6.4)			

[a] van Spronsen et al. 1994.
Sources: European Medicines Agency report,[2] FDA medical review,[3] Larochelle 2012,[4] van Spronsen et al. (1994).[5]

Liver Transplantation

In the NTBC study, 27 (13%) liver transplantations were performed: 20 for liver failure, HCC, or suspected HCC, and seven for elective transplantations (Table 8). In the historical control, 26 patients (25%) underwent liver transplantation for end-stage liver disease, porphyria symptoms, verified or presumed HCC, or elective surgery.[3]

In the Quebec study, more liver transplantations were performed for patients with restricted diet alone (71%) compared with those received nitisinone after 30 days of age. In the group that received nitisinone before 30 days of age, no patients required liver transplantation during the study.

Table 8: Liver Transplantation (n, %)

	The NTBC Study		The Quebec Study		
Study Population	**Nitisinone + Dietary Restriction**	**Dietary Restriction Alone (Historical Control)[a]**	**Nitisinone-Naive (Historical Control)**	**Late Treatment**	**Early Treatment**
	207	108	28	26	24
Overall	27 (13)	26 (25)	20 (71)	7 (26.9)	0
Transplant for liver failure	7 (3)	7 (6%) for end-stage liver disease; 5 (5%) for combination of end-stage liver disease and porphyria symptoms; 4 (4%) for HCC; 6 (6%) for suspected HCC, which was not verified at time of transplant; 4 (4%) elective transplant.	13 for cirrhosis or cancer, 5 for neurological crises.	7 for cirrhosis	
Transplant for HCC	7 (3)				
Transplant for suspected HCC, not verified	6 (3)				
Elective transplant	7 (3)				

HCC = hepatocellular carcinoma.

[a] van Spronsen et al. 1994.
Sources: European Medicines Agency report,[2] FDA medical review,[3] Larochelle 2012,[4] van Spronsen el al. (1994).[5]

Hepatocellular Carcinoma

A total of 10 patients (5%) in the NTBC study developed HCC, which occurred at 0.5, 4, 9, 10, 10, 12, 18, 30, 32, and 42 months after starting therapy with nitisinone. All patients were older than one year of age except one.[3]

In the NTBC study, the cumulative probability of death due to HCC, transplantation due to HCC, or diagnosis of HCC for all patients who started nitisinone treatment after two years of age was 8%, 12% and 27% at one, two, and four years, respectively. For patients who started nitisinone treatment before two years of age, this cumulative probability was 1% at all three time points.[2]

In the historical population, HCC developed in 8% of the patients.[5]

In the Quebec study, HCC was found at transplantation in a patient in the late-treatment group (3.8%).[4]

Health-Related Quality of Life

This outcome was not assessed in the included studies.

Porphyric Crisis

In the NTBC study, no cases of fatal porphyric crises were observed. One patient developed a mild porphyric crisis during the study.[3] In the historical population, 10% died from consequences of porphyria-like crises.[5]

In the Quebec study, patients in the nitisinone-naive group spent 71 months for neurologic crises in hospital, compared with 17 months in the late-treatment group and zero month in the early-treatment group.[4] The numbers of patients contributing to these events were not reported.

Biochemical Variables

The results of biochemical variables were not reported in sufficient details in the Quebec study. Results of the NTBC study are provided in Table 9.

Saccinylacetone

In the NTBC study, before treatment, urine SA varied from barely detectable to > 1,000 mmol/mol creatinine. In the main analysis, urine SA was reduced to below the reference limit (less than 1 mmol/mol creatinine) within 0.3 months after start of the nitisinone therapy. Plasma SA also decreased to below the reference limit (< 0.1 µmol/L) with a median time to normalization of 3.9 months. In the complementary analysis, similar findings were reported.

Tyrosine

After one year of treatment, the plasma level of tyrosine increased from 140 µmol/L to 387 µmol/L.

Liver Function

After one year of treatment, the median serum alanine transaminase level increased by 30%, but the level of aspartate transaminase was lower than the pre-treatment values. At the start of therapy, the median of international normalized ratio was 1.675; this outcome

decreased to 1.15 (reference range 0.80 to 1.20) after one month of treatment. The median of alpha-fetoprotein (AFP) level decreased from 471 mcg/L before treatment to 3 mcg/L after one year of treatment.

Renal Function

The serum creatinine was within the normal range at pre-treatment and there was no significant change observed during the treatment of nitisinone. The median level of urine amino acids decreased from 7,535 mmol/mol creatinine before treatment to 1,372 mmol/mol creatinine after one year of treatment.

Hematologic

The neutrophil counts were within the normal range before the treatment. There was no significant change observed during the study. The median pre-treatment platelet count increased from 133,000/µL to 228,000/µL after one year of treatment.

Table 9: Laboratory Variables

	The NTBC Study		The Quebec Study		
Study Population	**207**		**Nitisinone-Naïve (n = 28)**	**Late Treatment (n = 26)**	**Early Treatment (n = 24)**
	Pre-Nitisinone-Treatment	**1-Year Visit**			
HT-1 specific biochemical variables					
Urine SA	> 90% of all patients normalized by 2 weeks (< 1 mmol/mol creatinine)		Urine SA levels decreased 7.3-fold 12 hours following the first dose of nitisinone; after 1 week of nitisinone therapy, urine SA levels were not significantly different from those ≥ 3 months later. Data were presented graphically.		
Plasma SA	> 80% of patients by 6 months (< 0.1 µmol/L)		NR		
Tyrosine (µmol/L), median	140 (n = 193)	387 (n = 114)	Tyrosine levels increased following nitisinone administration. Data were presented graphically.		
Liver function					
ALT (U/L), median	56	73	Liver function abnormalities were common before nitisinone treatment. In the late-treatment group levels of coagulopathy, ALT and AST normalized by 4 months of treatment. No data were reported for patients in the nitisinone-naive group and the early-treatment group. Elevated pre-treatment AFP levels were observed for all patients, and typically normalized during the second year of treatment. No other details were provided.		
AST (U/L), median	90	77			
INR, median	1.675 in 60 patients	1.15 in 51 patients after 1 month treatment			
AFP (µg/L), median	471	3 (in 8/11 patients, AFP concentration increased suddenly, HCC was verified by histopathology)			
Renal function					
Serum creatinine	Within the normal range	No significant changes were observed	No renal failure was developed during treatment.		
Urine amino acids (mmol/mol creatinine)	7,535 (this outcome was followed only in patients with elevated levels at pre-treatment, n = 13)	1,372			

	The NTBC Study		The Quebec Study		
Study Population	**207**		**Nitisinone-Naïve**	**Late**	**Early**
Hematologic					
Neutrophil counts	Within the normal range	No significant changes were observed	It is indicated that complete blood counts showed no consistent or sustained abnormality. Detailed results were not reported.		
Platelet counts (/µL), median	133,000 (n = 127)	228,000 (n = 53)			

AFP = alpha-fetoprotein; ALT = alanine transaminase; AST = aspartate transaminase; HCC = hepatocellular carcinoma; HT-1 = hereditary tyrosinemia type I; INR = international normalized ratio; NR = not reported; SA = saccinylacetone.

Sources: FDA medical review,[3] Larochelle 2012.[4]

Hospitalization Resulting From Acute Complications of HT-1

In the Quebec study, patients in the nitisinone-naive group and those in the pre-nitisinone period of the later-treatment group spent a total of 56 out of 784 total follow-up months in the hospital. There were no patients developed an acute HT-1-related complication while treated with nitisinone.[4]

Harms

Only those harms identified in the review protocol are reported below (Table 2).

Adverse Events

The occurrence of overall AEs in the NTBC main analysis was not reported. In the complementary analysis of the NTBC study, 51.2% (128 of 250) of patients experienced at least one AE.[25] Eye disorders (conjunctivitis, blepharitis, keratitis, eye pain, photophobia, and corneal opacity with symptoms of itching, burning, photophobia, corneal erosion, and corneal clouding) were the most commonly reported AEs, with 31 events observed in 14 patients.[3]

Transient thrombocytopenia, neutropenia, or both were reported in 3%, 3%, and 1.5% of the study population, while there were no infections or bleeding that could be ascribed to the observed neutropenia or thrombocytopenia. Details of the harm data in the NTBC study are presented in Table 10.

In the Quebec study, one patient developed photophobia and corneal crystals, which disappeared within 24 hours of strict dietary restriction.

Serious Adverse Events

In the main analysis of the NTBC study, 49 SAEs were reported, including liver failure (14), HCC (10 verified, six not verified), multi-organ failure (one), elective liver transplantation (seven), and thrombocytopenia (three). The three cases of thrombocytopenia, which were all transient, were the only SAEs considered to have a possible relationship to nitisinone, whereas the other aforementioned events were reported by the investigators as likely to be related to the underlying disease and not nitisinone treatment.[2]

The Quebec study did not report data on SAEs.

Withdrawals Due to Adverse Events

In the main analysis of the NTBC study, no patient has been withdrawn because of AEs of the drug. No data were reported for WDAEs in the Quebec study.

Mortality

During the treatment with nitisinone in the NTBC study, there were 10 deaths reported in the main analysis of the NTBC study, due to liver failure (seven patients), HCC (two) and multi-organ failure (one).[2] In the complementary analysis, 15 deaths (6.0%) in 250 patients treated with nitisinone were reported, due to liver failure (eight), HCC (two), multi-organ failure (two), gastrointestinal bleeding (one), complications of prematurity (one) and unspecified reason (one).[25]

In the Quebec study, 10 patients in the never-treated group died, while two patients in the late-treatment group died during the study.[4]

Notable Harms

In the NTBC study, the tyrosine concentration was described as “tends to be higher in patients with eye symptoms.” No details were reported. Several patients with reported or occasional tyrosine levels above 1,000 µmol/L had not experienced any eye symptoms. The median of tyrosine concentration increased from 140 µmol/L to 387 µmol/L after one year of treatment with nitisinone.

In the Quebec study, 12 episodes of asymptomatic elevations of ALT level ≥ 60 U/L were reported, but they all spontaneously resolved without changes in dose of the study drug.

Table 10: Harms

	The NTBC Study (N = 207)
AEs[a]	
Subjects with > 0 AEs, n (%)	NR
Thrombocytopenia	6 (3)
Dermatitis exfoliative	2 (1)
Pruritus	3 (1.4)
Granulocytopenia	2 (1)
Leucopenia	4 (2)
Blepharitis	2 (1)
Conjunctivitis	4 (2)
Corneal opacity	4 (2)
Eye pain	3 (1.2)
keratitis	5 (2)
Photophobia	4 (2)
SAEs, n (%)	
Severe thrombocytopenia	3 (1.4)[b]
WDAEs, n (%)	
	0
Deaths, n (%)	
10 (4.8)	Liver failure 7 (3.4) HCC 2 (1.0) Multi-organ failure (0.5)

AE = adverse event; HCC = hepatocellular carcinoma; NR = not reported; SAE = serious adverse event; WDAE = withdrawal due to adverse event.

[a] May be causally related to treatment with nitisinone.

[b] 49 SAEs were reported, while three of them were considered to be treatment-related.

Source: European Medicines Agency report.[2]

Discussion

Summary of Available Evidence

Two manufacturer-submitted, single-arm, open-label studies were included in this review to provide evidence for the clinical efficacy and safety of nitisinone in patients with HT-1. The NTBC study (N = 207 in the main analysis) enrolled patients from 25 countries, including Canada (39 patients), between February 1991 and August 1997. Patients were diagnosed by the presence of SA in the urine or plasma. In the main analysis of the NTBC study, 207 patients received nitisinone at a starting dosage of 0.6 to 1 mg/kg/day; a complementary analysis was performed on 250 patients who received nitisinone at the currently recommended starting dosage of 1 mg/kg/day. The NTBC study has been conducted over nine years. Results of the NTBC study were compared with a historical population that received the dietary treatment alone. The study protocol required that laboratory and clinical data be reported to a common database in Gothenburg, Sweden, and that urine and blood samples be sent there for measurement of critical variables. A patient group participating in an international survey was used as the historical control for the NTBC study. All these patients received dietary treatment alone. The study of the historical control was published in 1994, although the time period in which the study participants were enrolled was not specified. In the Quebec study (N = 78), the outcomes of children born during the first 10 years that nitisinone became available in Quebec were compared with those of patients born in the preceding decade, during which all current treatment options except nitisinone were available. Nitisinone was initially administered at 0.6 or 1 mg/kg/day, and it has been increased to 1 mg/kg/day after the first few years of the study. Nitisinone-treated patients were compared with those who never received nitisinone therapy, in the same centre. Survival probability, occurrence of liver failure, requirement of liver transplantation, development of HCC, porphyric crises, hospitalization due to acute HT-1-related complications, and biochemical variables related to HT-1 were examined.

The main limitation was that both studies were single-arm, and the clinical benefits and harms of nitisinone in combination of dietary restriction of tyrosine and phenylalanine were examined by comparing with a historical control. No formal statistical test was performed on the outcomes between treatment and control. No precise estimates of treatment effects of dietary restriction plus nitisinone relative to dietary restriction alone were produced. In addition, significant heterogeneity was observed between patients treated with nitisinone in combination with dietary restriction and the historical control (dietary restriction alone). Therefore, this renders it difficult to assess the benefit of nitisinone in combination with dietary restriction, although a protective effect on a series of pre-specified clinically relevant long-term outcomes, such as survival and liver and renal functions are highly likely. Given the nature of such a severe, life-threatening, rare disease, such a single-arm trial design seems acceptable.

Interpretation of Results

Efficacy

In general, survival probability was higher in patients treated with nitisinone. In the NTBC study, the two-year and four-year overall survival rates for patients who initiated nitisinone at any age were 96% and 93%, respectively. In addition, survival probability was explored in subgroups based on the age of starting nitisinone treatment. For patients who started

before two months of age, their two-year and four-year overall survival rates were 88% and 88%, respectively; for those who started before six months of age, the two-year and four-year overall survival rates were 94% and 94%, respectively; for those who started after six months of age, the two-year and four-year overall survival rates were 97% and 93%, respectively. Results of the complementary analysis were similar to those in the main analysis: the overall survival rate for patients who initiated nitisinone at any age was 93% at two years, four years, and six years. In the historical population that received dietary treatment alone, the two-year survival rates were 29%, 74%, and 96% for patients in whom symptoms developed before two months, from two to six months, and after six months of age, respectively. The four-year survival rate was similar to the two-year survival rate in the historical population, for all three subgroups of patients. The results suggest that nitisinone in combination with dietary restriction has a benefit on survival compared with dietary restriction alone if started before two months of age. The results of the NTBC study were supported by the Quebec study, in which higher mortality rates were observed in patients who never received nitisinone treatment compared with those treated with nitisinone. Similar benefits were observed for liver failure–related death. Results of the NTBC study showed that the four-year cumulative probability of death or transplantation due to liver failure was 13%, while in the historical population, approximately 32% of the patients died due to liver failure or recurrent bleeding, or were transplanted due to liver failure.

Patients treated with nitisinone had a lower risk of death or transplantation due to liver failure. In the NTBC study, seven patients (3.4%) died of liver failure and seven transplantations (3.4%) were performed due to liver failure (i.e., approximately 7% in total). For patients with treatment started before six months of age, 9% died of liver failure or were transplanted due to liver failure. In the historical control, 25% of patients died of liver failure and transplantation due to liver failure was performed in six of 108 (6.4%) patients. For patients in the historical cohort with symptom onset before six months, 42% died of liver failure or recurrent bleeding with or without liver failure. The results imply that treatment with nitisinone reduces the risk of fatal liver disease in patients presenting with the acute form of HT-1 before six months of age. In the Quebec study, no early-treated patients had developed detectable liver disease after more than five years of treatment.

Nitisinone-treated patients required fewer liver transplantations compared with those received dietary restriction alone. The NTBC study reported that liver transplantation was performed in 13% of the study participants, while in the historical control, 25% underwent the procedure. In the Quebec study, more liver transplantations were performed for patients not treated with nitisinone, compared with those who received nitisinone after 30 days of age. In the group that received nitisinone before 30 days of age, no transplantations were needed.

Treatment with nitisinone was also related to lower incidence of HCC: 5% of the patients in the NTBC study developed HCC compared with 8% in the historical control. In the NTBC study, all patients diagnosed with HCC were older than one year of age except one. Early detection of HCC is a priority for the clinical management of HT-1. Although the results suggest a benefit with nitisinone treatment reducing the occurrence of HCC, the results still indicate that even if non-transplanted HT-1 patients have been treated by nitisinone, they are still considered to be at risk and need to be followed for the development of HCC.

In addition, the data suggest that nitisinone is associated with decreased risk of porphyric crises and fewer hospitalizations related to HT-1 complications.

Both studies reviewed were approximately 10 years in duration. However, the extent to which the potential survival and morbidity benefits of nitisinone over dietary restriction alone would be maintained beyond the duration of the studies is uncertain.

Before treatment with nitisinone, urine SA varied from barely detectable to greater than 1,000 mmol/mol creatinine. Shortly after the start of nitisinone, urine SA was reduced to below the reference limit for the laboratory test (< 1 mmol/mol creatinine). According to previous research, SA levels must be near or below the detection limit of standard assays to demonstrate an optimal treatment effect, although no formal minimal clinically important difference (MCID) has been established for SA concentrations in the urine or blood (Appendix 4).

Nitisinone was associated with increased plasma levels of tyrosine and decreased AFP levels. There was no significant change in the serum creatinine levels but the level of urine amino acids decreased after one year of treatment. The platelet count increased as well after one year of treatment.

Harms

In the NTBC study, eye disorders (conjunctivitis, blepharitis, keratitis, eye pain, photophobia, and corneal opacity with symptoms of itching, burning, photophobia, corneal erosion, and corneal clouding) were the most commonly reported AEs, with 31 events observed in 14 patients. In the Quebec study, one patient developed photophobia and corneal crystals, which disappeared within 24 hours of strict dietary restriction. Transient thrombocytopenia, neutropenia, or both were reported in 3%, 3%, and 1.5% of the study population, while there were no infections or bleeding that could be ascribed to the observed neutropenia or thrombocytopenia.

In the NTBC study, 49 SAEs were reported, but most were considered to be related to the underlying disease and not nitisinone treatment by the investigators. Of the 49 SAEs, three cases of severe thrombocytopenia were deemed to be related to the treatment of nitisinone. No patient has been withdrawn because of AEs of nitisinone in the NTBC study. Ten deaths in the NTBC study and two in the Quebec study were reported. Due to the lack of information on treatment adherence, it is not possible to examine the relationship between treatment effect (on survival or other clinically important outcomes) and treatment adherence.

Potential Place in Therapy[a]

Although HT-1 is a pan-ethnic disease worldwide, in Canada the highest incidence is found in French-Canadian descendants from the Saguenay–Lac-St-Jean region in Quebec. In this population, HT-1 is a severe disease that presents in early infancy with any combination of chronic hepatopathy, failure to thrive, renal insufficiency, and neurological disease with pain crises. The natural course of the disease is degenerative, leading to liver failure, hepatocellular carcinoma, hypertension, renal failure, and hypophosphatemic rickets. Patients often die in childhood, with 60% mortality by one year of age if symptoms present before two months of age.[5] There is no cure. Early attempts at treatment included diet therapy with tyrosine and phenylalanine restriction, which can improve the kidney disease and temporarily relieve some of the neurological symptoms, but individuals can still develop liver cancer and have reduced life expectancy later in childhood. Liver failure or cancer

[a] This information is based on information provided in draft form by the clinical expert consulted by CDR reviewers for the purpose of this review.

(HCC) has been treated with a liver transplant, but this is not completely effective in cases with advanced symptoms at the time of transplant; patients require immunosuppression and deaths can occur after transplant from surgical complications, organ rejection, severe underlying disease, or undetected metastatic disease. Therefore, there is a significant unmet medical need for an agent that can effectively reduce the complications of the disease, improve quality of life, reduce the risk of developing liver disease and cancer, and improve life expectancy.

Nitisinone is typically started at a dosage of 1 mg/kg/day of nitisinone, which in practice is often sufficient to improve clinical symptoms, but higher dosages of up to 2 mg/kg/day may be needed to eliminate detection of SA in the urine in acute crises. Adult patients or those with a high body mass index may be dosed at 35 mg/m^2 body surface area per day. A typical target range of plasma nitisinone is 30 µmol/L to 50 µmol/L.

Nitisinone can increase tyrosine levels in the blood, which can lead to corneal opacities and hyperkeratotic lesions of the palms and soles. High tyrosine levels can also lead to neurological symptoms. The increased tyrosine levels can be treated with a tyrosine-restricted diet. Plasma tyrosine levels should be kept below 500 µmol/L. Nitisinone can lead to eye symptoms, such as itching, burning, or photophobia, and corneal opacification. Developmental delay has been detected in patients using nitisinone, although it is not clear if this is because they are surviving and it is the natural history of the disease, or if it is dietary restriction or the elevated tyrosine levels that result with nitisinone use. Rarer hematologic side effects include leucopenia and thrombocytopenia. Gastrointestinal upset has also been reported.

It seems clear that pre-symptomatic diagnosis and treatment produces the best outcome, which can be accomplished by newborn screening, which is performed in Quebec, but not in all provinces.

It is possible not all patients respond to nitisinone, especially when treatment is delayed, and even in those with improvement in hepatocellular disease and decline in serum AFP levels can later develop hepatocellular carcinoma, and they should continue to be monitored. Based on the reviewed data, it appears very rare for HCC to develop with early onset of therapy within the first two months of life.

Monitoring of patients should be performed in centres with clinicians familiar with the management of HT-1. Nitisinone treatment should not be interrupted and can be continued even if a patient receives a liver transplant. Most centres monitor SA levels, plasma amino acids, liver enzymes, alkaline phosphatase, complete blood count, AFP, and neurocognitive assessment and use regular tumour-surveillance imaging.

No proven clinical benefit has been published for the use of nitisinone in alkaptonuria, and nitisinone is not indicated for other types of tyrosinemia.

Conclusions

Two manufacturer-submitted, single-arm, open-label studies demonstrated an association between treatment with nitisinone in combination of dietary restriction of tyrosine and phenylalanine and improved survival in patients with HT-1 as compared with a historical population that received dietary treatment alone. Greater survival benefits were observed in patients who started treatment before two months of age. Nitisinone was also associated with reduced risk of liver failure, fewer liver transplantation requirements, lower risk of HCC, fewer porphyric crises, and reduced acute complications of HT-1. Delayed nitisinone treatment (i.e., beyond six months of age) was associated with an increased risk of HCC and requirement for liver transplant. Eye disorders related to elevated plasma tyrosine levels with nitisinone treatment were the most commonly reported AEs. Thrombocytopenia and neutropenia may also occur with nitisinone treatment, although no serious sequelae were identified in the studies. Most of the reported serious adverse events were considered to likely be related to the underlying disease and not nitisinone.

The included studies were limited by the open-label design and lack of a direct comparator. Moreover, no absolute or relative measures of effect with formal statistical comparisons were performed on the outcomes between nitisinone plus dietary restriction versus dietary restriction alone, and therefore there is uncertainty as to the magnitude of any benefit with nitisinone as compared with dietary restriction. However, the relatively large difference in survival probabilities (primarily if initiated in those younger than six months) and reduced morbidity as compared with an historical control suggest there is an overall clinically significant beneficial effect with nitisinone in treating patients with HT-1, although the extent to which this would be maintained over a lifetime (approximately 80 years, based on Canadian general population estimates) is associated with uncertainty.

Appendix 1: Patient Input Summary

This section was prepared by CADTH staff based on the input provided by patient groups.

1. Brief Description of Patient Group(s) Supplying Input

Two groups, the Canadian Liver Foundation (CLF) and the Canadian Organization for Rare Disorders (CORD), submitted patient input for this summary.

The CLF is a national charity dedicated to improving the health and outcomes of Canadians living with, or at risk of, various forms of liver disease. The organization funds research programs aimed at discovering the causes, preventive measures, and potential treatments for liver disease. It supports public and professional education and patient support programs, and engages in fundraising, outreach, and advocacy efforts. The CLF receives program funding in the form of unrestricted educational grants from pharmaceutical companies, but no companies with direct or indirect interests in the drug under review provided any financial support within the last two years. The majority of awareness, education, patient support, and research grant programs is funded by donations from individuals. The group disclosed no conflicts of interest in the preparation of the submission. The information for this submission was collected via a bilingual online questionnaire offered to patients, caregivers, and health care professionals across Canada. Six patients with hereditary tyrosinemia type 1 (HT-1), 36 caregivers, and four health professionals responded to the questionnaire.

CORD is registered charity that advocates health policies and a health care system that work for those with rare disorders. CORD provides education and resources to patient groups to enable them to better meet their members' needs. CORD did not receive help outside its patient group in completing, or in collecting and analyzing information for, this patient submission. The group did declare a financial payment from Sobi (the manufacturer of Orfadin), in the range of $0 to $5,000 within the last two years. CORD collected information for this submission from interviews with three parents of patients and two metabolic-clinic nurses. An online survey was also available, to which 12 responded (11 parents and one patient), eight of whom represented Canadian patients. All respondents were diagnosed with HT-1: 75% had acute and 25% had chronic conditions. All forms of nitisinone were included in the CORD submission.

2. Condition-Related Information

HT-1 is a rare, inborn genetic error of metabolism associated with a severe form of liver disease in infancy or early childhood. According to CLF, one in 100,000 individuals is affected globally, but in the Saguenay–Lac-St-Jean region of Quebec, one person in 20 is a carrier and one in 1,846 has HT-1. In its acute form, the disease manifests within the first month of life. Symptoms may include poor weight gain, an enlarged liver and spleen, a distended abdomen, swollen legs, an increased tendency to bleed, and jaundice. Without drug or transplant treatment, death from hepatic failure frequently occurs within three to nine months of birth. The onset of chronic HT-1 is more gradual, and the clinical manifestations are less severe. Common symptoms in these children include enlarged liver and spleen, distended abdomen, poor weight gain, and frequent vomiting and diarrhea. Affected patients usually develop cirrhosis and its complications. Without treatment, these children may develop liver cancer or liver failure and require a liver transplant.

Patient experiences can be categorized either by the form of disease (acute versus chronic) or by the era in which the patient was born (this can relate to the availability of treatment options or to the advent of newborn screening programs). In all cases, it is apparent that patients have the best chance of survival and the fewest long-term complications when they are diagnosed within days of birth and can begin treatment programs immediately upon diagnosis.

Patients' and caregivers' lives frequently revolve around the burdens of this disease. Financial, social, and emotional strains may be experienced by the entire family of tyrosinemia patients. Respondents described the impact of HT-1 on their families: "cooking 8 different kinds of meals per day; not able to work on a regular basis; watching children 24/7 to make sure that they don't eat restricted food; regular hospital visits; lack of a social life — avoiding large family and friends gatherings; financial hardship; building kids' personality — training them to accept themselves as being different from other children; food training — what to eat and what not to eat; school training — ensuring school environment understands and respects the importance of adherence to regimen…." The demanding treatment regimen, addressed in the next section, represents another set of burdens for patients and caregivers.

3. Current Therapy-Related Information

Prior to the availability of nitisinone in the 1990s, the only treatment options for HT-1 were a strict low-protein diet (low in phenylalanine and tyrosine) and, later, liver transplant. Even on a low-protein diet, some patients awaiting transplant struggled to survive. Without treatment, the disease was almost always fatal before the age of 10. For patients who have undergone liver transplant and who have survived into adulthood, uncertainty of life after transplant is a continued reality.

Most respondents are currently receiving the drug under review (Orfadin capsules or a bioequivalent version of the same drug) or had used it in the past. Nitisinone blocks the breakdown of tyrosine before it can be converted into a harmful product. Patients often respond quickly: blood clotting issues resolve and liver function improves within one week of treatment. Starting nitisinone treatment immediately at diagnosis is a requisite part of the life-saving therapy. Patients experience the benefits of reduced hospitalizations, neurological crises, liver transplants, and other complications, without serious side effects from the treatment. The parents have hope of a future for these children. A pregnant patient from CLF stated that "I started treatment at the age of 5 and before that I experienced the disease with its negative effects with neurological crises and numerous hospitalizations. My life changed completely with the arrival of NTBC in 1993. It has been 22 years since I started taking the NTBC and I have not been hospitalized for the disease since that time."

While there is unanimous agreement that the nitisinone era has been life-saving and offers the opportunity to lead a more normal life, HT-1 still presents many challenges. Patients must adhere to the strict diet and be monitored regularly for progress. Once a patient is stable, monitoring can decrease in frequency, but the dietary restrictions and medical appointments can be taxing and costly. Another challenge is administrating the drug to infants: "It was hard when he was a baby to mix and syringe into his mouth after opening capsules." A range of experiences is reported in terms of how patients, caregivers, and families are affected by the disease and treatment requirements. Some report little disturbance to their lives, while others experience wide-reaching effects.

Some caregivers feel that life is far from normal, revolving around the demanding treatment schedule and dietary restrictions. Caregivers must ensure that every dose of medication is taken and that every meal is completed. This can be challenging and anxiety-provoking, particularly in newborns and infants, as children enter school (where mealtime is less controlled), and during the teenage years. Family and individual social lives may suffer. The financial impact can be significant. At times the caregiver demands are such that parents struggle to maintain a steady job. Patients also live with these restrictions, medical requirements, and complications that can affect their physical, social, emotional, and financial well-being. Despite treatment, one-third of all respondents in the CORD submission reported that their child was currently experiencing cognitive delay. The submission also highlighted a few minor side effects reported by about half of respondents using Orfadin capsules or oral suspension, including stomach bloating or pain, feeling tired or weak, or loss of appetite or weight. Even if the patient is taking nitisinone, long-term complications of the disease may still occur, most notably the development of liver cancer. However, respondents of both the CLF and CORD surveys generally struggled more with the diet component of the treatment than with the medication.

Finally, there is anxiety about receiving the medication in a timely fashion as any interruption in treatment has the potential for serious consequences. The submission from CORD further highlighted the frustration when an uncommunicated switch from one manufacturer of nitisinone to the other was implemented in Canada, and respondents were left wondering and worrying about the efficacy of the drug.

4. Expectations About the Drug Being Reviewed

Two slightly different messages were conveyed by the two patient groups. The somewhat different patient/caregiver experiences and expectations reported in these submissions may have to do with where the respondents live in Canada, as different provinces may offer different options to patients, possibly at different costs and through different access programs.

The CLF submission discussed the current availability of nitisinone through the Health Canada Special Access Programme, with patients receiving their medication from hospital pharmacies. Some respondents are content with this arrangement while others welcome more direct access to their medication through the public drug plans, allowing self-sufficient collection at their local pharmacy, rather than long-distance travel to hospitals.

The CORD submission put more emphasis on unmet needs and future expectations, including the desire for different formulations (e.g., an oral formulation for infants, a tablet rather than capsule option, increased medication stability, and improved taste), less frequent dosing, further research, and a medication that would allow a more normal diet. Finally, while all interview and survey respondents were satisfied with both available versions of nitisinone (MDK-nitisinone and Orfadin), all rated the availability of more than one form of nitisinone as “important” or “very important.”

Regardless of the program supporting the availability of nitisinone within Canada, there is a strong and clear message from patients, caregivers, and health care professionals alike. First, the cost to patients should remain low or non-existent. As this is a life-saving therapy, it is imperative to ensure that no patient is left untreated or has to assume an unfair financial burden. Second, universal accessibility and interruption-free availability of nitisinone will be critical (1) during any transition to the public drug plans in Canada and (2) throughout a patient’s lifetime.

Appendix 2: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to present Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present Note: Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	September 26, 2017
Alerts:	Weekly search updates until January 17, 2018
Study Types:	No search filters were applied
Limits:	No date or language limits were used Conference abstracts were excluded

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
.ti	Title
.ab	Abstract
.ot	Original title
.hw	Heading word; usually includes subject headings and controlled vocabulary
.kf	Author keyword heading word (MEDLINE)
.kw	Author keyword (Embase)
.rn	CAS registry number
.nm	Name of substance word
ppez	Ovid database code; Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
oemezd	Ovid database code; Embase 1974 to present, updated daily

MULTI-DATABASE STRATEGY	
#	**Embase, Ovid MEDLINE(R)**
1	(nitisinon* or nitison* or orfadin* or nityr* or ntbc or SC-0735 or SC0735 or K5BN214699 or 104206-65-7).ti,ab,ot,kf,hw,rn,nm.
2	1 use ppez
3	*nitisinone/
4	(nitisinon* or nitison* or orfadin* or nityr* or ntbc or SC-0735 or SC0735 or K5BN214699 or 104206-65-7).ti,ab,ot,kw.
5	3 or 4
6	5 use oemezd
7	conference abstract.pt.
8	6 not 7
9	2 or 8
10	remove duplicates from 9

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	
Trial registries (Clinicaltrials.gov and others)	Same keywords, limits used as per MEDLINE search.	

Grey Literature

Dates for Search:	September 2017
Keywords:	Drug name, Indication
Limits:	No date or language limits used

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Health Economics
- Clinical Practice Guidelines
- Drug and Device Regulatory Approvals
- Advisories and Warnings
- Drug Class Reviews
- Databases (free)
- Internet Search.

Appendix 3: Detailed Outcome Data

Table 11: Survival Probabilities After 2, 4, and 6 Years of Treatment with Nitisinone (%)

	The NTBC Study (Complementary Analysis)		
Study Population	250		
Survival	2 years	4 years	6 years
Overall	93	93	93
Start age 0 to 2 months	93	93	93
Start age 0 to 6 months	96	95	95
Start age > 6 months	94	94	94

Source: Product monograph of Orfadin.[19]

Appendix 4: Validity of Outcome Measures

Aim

To summarize the validity of the following outcome measures:

- Succinylacetone (blood and urine)
- Plasma tyrosine

Findings

Succinylacetone (Blood and Urine)

Hereditary tyrosinemia type 1 (HT-1) is caused by a deficiency in fumarylacetoacetate hydrolase (FAH), the final enzyme in the tyrosine catabolic pathway.[28-31] The substrates upstream of FAH in the metabolic pathway are maleylacetoacetate (MAA) and fumarylacetoacetate (FAA), both of which are reactive, toxic metabolites.[32-41] When FAH function is lacking, MAA and FAA are not metabolized via the tyrosine catabolic pathway, yet these unstable metabolites are generally not detectable in the urine or blood. In the absence of FAH, FAA, and MAA can undergo conversion to succinylacetoactetate (SAA) and, ultimately, to succinylacetone (SA) which is readily detectable in both urine and blood.[42,43] The FAA derivative SA has not been detected in any other diseases, thus it is considered pathognomonic for HT-1.[10,16,44] However, two rare FAH mutations have been reported in at least three individuals diagnosed with HT-1 who do not have elevated or detectable levels of SA.[45,46] Consensus group review in Canada and the US recommends that SA be measured in newborn screening programs to diagnose HT-1, and be further monitored in response to nitisinone treatment.[10] As of 2015, all Canadian provinces and territories, except for New Brunswick, Nova Scotia, and Prince Edward Island, were screening for HT-1 through their newborn screening programs.[17]

Dried blood spots extracted and analyzed by tandem mass spectrometry (MS/MS) are the optimal format for newborn screening.[10,15] A number of different assays are currently in use worldwide and while studies suggest that these are highly specific and sensitive for HT-1,[15,47] the nature of these studies is biased, which limits the accurate determination of specificity, sensitivity, positive predictive value, and negative predictive value.[15] Briefly, cut-off values for SA in newborn screening varied from 1.29 µmol/L to 10 µmol/L. In studies reporting screening experiences, the positive predictive values for the SA test ranged from 66.7% (among ~500,000 screened individuals) to 100% (among ~850,000 screened individuals), but these were associated with large confidence intervals due to the small number of cases. Sensitivity and specificity could not be determined due to lack of follow-up of those with negative screening results. Among case-control studies, the sensitivity (in five studies) and specificity (in four studies) for the test were each reported at 100%. All of the studies evaluating SA assays were at moderate to high risk of bias due to a number of factors. The results of the screening studies were weakened by a lack of adequate follow-up subsequent to a negative screening result and concerns related to the reference standard. The case-control studies present a number of weaknesses, including retrospectively specified cut-offs, unblinded assessors, different reference standards across participants within a study, and insufficient reporting of reference standards. Furthermore, each study used unique cut-off values and different recovery methods and collection times, limiting the comparability of these studies and a comprehensive understanding of newborn SA levels and their relationship to HT-1.[15] While there is no standard method for newborn

HT-1 screening, the available studies do suggest that SA in dried blood spots analyzed by MS/MS may provide sufficient precision to differentiate between non-cases and probable cases of HT-1.[15,47]

Following newborn screening, or clinical presentation with symptoms of HT-1, confirmatory presence of SA in blood, or in urine when blood is not available, is considered diagnostic of HT-1. However, SA testing should be accompanied by further biochemical laboratory tests and corroborated by sequence analysis of the FAH gene before a diagnosis of HT-1 is concluded.[10]

As the definitive biochemical marker of the HT-1 phenotype, monitoring the decrease or complete disappearance of SA is the standard practice used to confirm a patient's clinical improvement in response to nitisinone. Absence of SA in blood and urine suggests a complete, or near complete, block of a more proximal step in the tyrosine catabolic pathway, preventing the formation of MAA and FAA and their toxic by-products, SAA and SA. Although no formal minimal clinically important difference (MCID) exists for SA concentrations in the urine or blood, there is no indication that any level of these metabolites is safe. Thus, clinical consensus is that treatment goals should aim to suppress SA formation.[10] Multi-year cohort studies suggest that by adopting this course of action, HT-1 symptoms and complications can be slowed or avoided in most patients.[4,23,24,48]

SA values quantified from urine and blood will depend on the assay format and sensitivity of the reporting laboratory. The reference limits for normal plasma SA levels may be reported as < 0.1 µmol/L; normal urine SA levels as < 1 mmol/mol creatinine.[2,3,10,23,24] Less sensitive assays may report normal SA levels as undetectable.[10] SA can be volatile and improper test conditions can prevent detection. Dilute urine, improper handling of urine samples, and certain methods of extraction can lead to false negatives. Thus, an understanding of the assay and proper sample handling and preparation is imperative to interpretation of the results.[10,15,49,50]

The manufacturer for nitisinone did not provide information regarding the sensitivity, specificity, or positive and negative predictive values for assays to measure SA from dried blood spots, plasma, or urine.

Plasma Tyrosine

SA in the blood and urine is the definitive biochemical marker for diagnosis of HT-1.[10] Tyrosine levels are neither a specific nor a sensitive marker of HT-1, as elevated plasma tyrosine may be identified in cases of hereditary tyrosinemia types 2 and 3 and in transient hypertyrosinemia.[10,51-53] Furthermore, some newborns with normal tyrosine levels have been diagnosed with HT-1 based on elevated SA concentrations and/or genetic confirmation.[46,53-55] Not every country nor region screens for SA, but may measure tyrosine levels. The normal range for plasma tyrosine is about 30 µmol/L to 120 µmol/L.[6] In newborns the mean tyrosine concentration may be slightly higher.[56] When elevated tyrosine levels (> 200 µmol/L or 250 µmol/L) are measured, an SA test can confirm or rule out HT-1. In newborn screening programs, both tyrosine and SA tests may be standard practice.[6,55] However, plasma tyrosine levels are only considered supportive of a diagnosis, as they are non-specific to HT-1.[10,15,47]

Once a diagnosis of HT-1 is made, and nitisinone treatment and dietary restriction are initiated, plasma tyrosine levels must be monitored to ensure that tyrosine accumulation in the blood, due to inhibition of 4-hydroxyphenylpyruvate dioxygenase in the proximal tyrosine catabolic pathway, does not exceed 500 µmol/L or 600 µmol/L.[6,10,24] Nitisinone

treatment results in elevated tyrosine levels that can be acceptably managed by instituting a low-protein diet supplemented with controlled amino acid quantities, to limit the amount of tyrosine that builds up in the bloodstream. While it is difficult to maintain a normal tyrosine plasma concentration range while on nitisinone treatment, it is hypothesized, based on other forms of hypertyrosinemia, that elevated tyrosine levels are not responsible for the phenotype of HT-1.[10,57-59]

There is no known MCID for tyrosine plasma concentrations, but generally, 200 µmol/L to 600 µmol/L is considered an acceptable range to limit the onset of clinical manifestations of elevated blood tyrosine.[10,16] Higher plasma tyrosine levels, as observed in HT-1, as well as in HT-1 treated patients who are non-responsive or non-adherent, can result in dermatological, ophthalmological, and possibly neurodevelopmental problems, although exact thresholds and symptoms may be patient-specific.[57-59] These side effects can generally be avoided and may be reversed by adherence to dietary restriction in combination with nitisinone treatment.[10,60-63]

References

1. Summary basis of decision (SBD) for Orfadin [Internet]. Ottawa: Health Canada; 2017. [cited 2017 Oct 23]. Available from: https://hpr-rps.hres.ca/reg-content/summary-basis-decision-detailTwo.php?linkID=SBD00344
2. Scientific discussion - Nitisinone [Internet]. London: European Medicines Agency; 2005. [cited 2017 Nov 23]. Available from: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000555/WC500049192.pdf
3. Center for Drug Evaluation and Research, U.S. Food and Drug Administration. Medical review(s). In: Orfadin™ (nitisinone). Company: Swedish Orphan AB. Application no.: 21-232. Approval date: 1/18/2002 [Internet]. Rockville (MD): FDA; 2001 Jun 2 [cited 2017 Oct 23]. (FDA drug approval package). Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-232_Orfadin.cfm
4. Larochelle J, Alvarez F, Bussieres JF, Chevalier I, Dallaire L, Dubois J, et al. Effect of nitisinone (NTBC) treatment on the clinical course of hepatorenal tyrosinemia in Quebec. Mol Genet Metab. 2012 Sep;107(1-2):49-54.
5. Van Spronsen FJ, Thomasse Y, Smit GP, Leonard JV, Clayton PT, Fidler V, et al. Hereditary tyrosinemia type I: a new clinical classification with difference in prognosis on dietary treatment. Hepatology. 1994 Nov;20(5):1187-91.
6. Grompe M. Disorders of tyrosine metabolism. In: Post TW, editor. UpToDate [Internet]. Waltham (MA): UpToDate; 2016 Dec 16 [cited 2017 Oct 23]. Available from: www.uptodate.com Subscription required.
7. Halac U, Dubois J, Mitchell GA. The liver in tyrosinemia type I: clinical management and course in Quebec. Adv Exp Med Biol. 2017;959:75-83.
8. Sniderman King L, Trahms C, Scott CR. Tyrosinemia type I. In: Adam MP, Ardinger HH, Pagon RA, Wallace SE, Bean LJH, Mefford HC, et al, editors. GeneReviews®. Seattle (WA): University of Washington; 2017 May 25.
9. McKiernan PJ. Nitisinone for the treatment of hereditary tyrosinemia type I. Expert Opin Orphan Drugs. 2013;1(6):491-7.
10. Chinsky JM, Singh R, Ficicioglu C, van Karnebeek CDM, Grompe M, Mitchell G, et al. Diagnosis and treatment of tyrosinemia type I: a US and Canadian consensus group review and recommendations. Genet Med. 2017 Aug 3.
11. Das AM. Clinical utility of nitisinone for the treatment of hereditary tyrosinemia type-1 (HT-1). Appl Clin Genet [Internet]. 2017 [cited 2017 Oct 23];10:43-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5533484
12. Paradis K. Tyrosinemia: the Quebec experience. Clin Invest Med. 1996 Oct;19(5):311-6.
13. Roth DS. Tyrosinemia. In: Medscape [Internet]. New York (NY): Mescape LLC; 2017 Aug 8 [cited 2017 Oct 23]. Available from: https://emedicine.medscape.com/article/949816-overview
14. rightdiagnosis.com [Internet]. [place unknown]: Health Grades Inc. Statistics by country for hepatorenal tyrosinemia; 2015 [cited 2017 Nov 23]. Available from: http://www.rightdiagnosis.com/h/hepatorenal_tyrosinemia/stats-country.htm#extrapwarning
15. Stinton C, Geppert J, Freeman K, Clarke A, Johnson S, Fraser H, et al. Newborn screening for Tyrosinemia type 1 using succinylacetone - a systematic review of test accuracy. Orphanet J Rare Dis [Internet]. 2017 Mar 9 [cited 2017 Oct 23];12(1):48. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5343414
16. Quebec Study Group, Alvarez F, Atkinson S, Bouchard M, Brunel-Guitton C, Buhas D, et al. The Quebec Study. Adv Exp Med Biol. 2017;959:187-95.
17. Newborn screening in Canada status report [Internet]. Toronto: Canadian Organization for Rare Disorders (CORD); 2015 Sep 3. [cited 2017 Nov 23]. Available from: https://www.raredisorders.ca/content/uploads/Canada-NBS-status-updated-Sept.-3-2015.pdf
18. Mitchell GA, Yang H. Remaining challenges in the treatment of tyrosinemia from the clinician's viewpoint. Adv Exp Med Biol. 2017;959:205-13.
19. Orfadin (nitisinone): 2 mg, 5 mg, 10 mg and 20 mg capsules [product monograph]. Stockholm: Swedish Orphan Biovitrum AB (publ); 2017 Nov 10.
20. Swedish Orphan Biovitrum (SOBI). Prescribing information: Orfadin® (nitisinone) capsules, for oral use [Internet]. Silver Spring (MD): U.S. Food and Drug Administration; 2017 Sep. [cited 2017 Oct 23]. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021232s020lbl.pdf
21. CDR submission: Orfadin (nitisinone), 2 mg, 5 mg, 10 mg and 20 mg capsules. Company: SOBI Canada Inc. [**CONFIDENTIAL** manufacturer's submission]. Oakville (ON): SOBI Canada Inc.; 2017 Aug 28.
22. Health Canada new drug authorizations: 2016 highlights [Internet]. Ottawa: Health Canada; 2017 Oct 24. [cited 2017 Nov 23]. Available from: https://www.canada.ca/en/health-canada/services/publications/drugs-health-products/health-canada-new-drug-authorizations-2016-highlights.html#a4
23. Holme E, Lindstedt S. Tyrosinaemia type I and NTBC (2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione). J Inherit Metab Dis. 1998 Aug;21(5):507-17.
24. Holme E, Lindstedt S. Nontransplant treatment of tyrosinemia. Clin Liver Dis. 2000 Nov;4(4):805-14.
25. Therapeutic Goods Administration. Australian public assessment report for nitisinone [Internet]. Woden ACT (AU): Government of Australia; 2011 Jan 13. [cited 2017 Nov 16]. Available from: https://www.tga.gov.au/sites/default/files/auspar-orfadin.pdf
26. Lindstedt S, Holme E, Lock EA, Hjalmarson O, Strandvik B. Treatment of hereditary tyrosinaemia type I by inhibition of 4-hydroxyphenylpyruvate dioxygenase. Lancet. 1992 Oct 3;340(8823):813-7.

27. Malik S, NiMhurchadha S, Jackson C, Eliasson L, Weinman J, Roche S, et al. Treatment adherence in type 1 hereditary tyrosinaemia (HT1): a mixed-method investigation into the beliefs, attitudes and behaviour of adolescent patients, their families and their health-care team. JIMD Rep [Internet]. 2015 [cited 2017 Oct 18];18:13-22. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4361919/pdf/978-3-662-44863-2_Chapter_337.pdf

28. Lindblad B, Lindstedt S, Steen G. On the enzymic defects in hereditary tyrosinemia. Proc Natl Acad Sci U S A [Internet]. 1977 Oct [cited 2017 Oct 27];74(10):4641-5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC432003

29. Fallstrom SP, Lindblad B, Lindstedt S, Steen G. Hereditary tyrosinemia - fumarylacetoacetase deficiency [abstract]. Pediatr Res [Internet]. 1979 [cited 2017 Oct 27];13:78. Available from: http://www.nature.com/pr/journal/v13/n1/pdf/pr197956a.pdf

30. Berger R, Smit GP, Stoker-de Vries SA, Duran M, Ketting D, Wadman SK. Deficiency of fumarylacetoacetase in a patient with hereditary tyrosinemia. Clin Chim Acta. 1981 Jul 18;114(1):37-44.

31. Kvittingen EA, Jellum E, Stokke O. Assay of fumarylacetoacetate fumarylhydrolase in human liver-deficient activity in a case of hereditary tyrosinemia. Clin Chim Acta. 1981 Sep;115(3):311-9.

32. Ruppert S, Kelsey G, Schedl A, Schmid E, Thies E, Schutz G. Deficiency of an enzyme of tyrosine metabolism underlies altered gene expression in newborn liver of lethal albino mice. Genes Dev. 1992 Aug;6(8):1430-43.

33. Jorquera R, Tanguay RM. The mutagenicity of the tyrosine metabolite, fumarylacetoacetate, is enhanced by glutathione depletion. Biochem Biophys Res Commun. 1997 Mar 6;232(1):42-8.

34. Jorquera R, Tanguay RM. Fumarylacetoacetate, the metabolite accumulating in hereditary tyrosinemia, activates the ERK pathway and induces mitotic abnormalities and genomic instability. Hum Mol Genet. 2001 Aug 15;10(17):1741-52.

35. Jorquera R, Tanguay RM. Cyclin B-dependent kinase and caspase-1 activation precedes mitochondrial dysfunction in fumarylacetoacetate-induced apoptosis. FASEB J. 1999 Dec;13(15):2284-98.

36. Kubo S, Sun M, Miyahara M, Umeyama K, Urakami K, Yamamoto T, et al. Hepatocyte injury in tyrosinemia type 1 is induced by fumarylacetoacetate and is inhibited by caspase inhibitors. Proc Natl Acad Sci U S A [Internet]. 1998 Aug 4 [cited 2017 Oct 27];95(16):9552-7. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC21376

37. Luijerink MC, Jacobs SM, van Beurden EA, Koornneef LP, Klomp LW, Berger R, et al. Extensive changes in liver gene expression induced by hereditary tyrosinemia type I are not normalized by treatment with 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione (NTBC). J Hepatol. 2003 Dec;39(6):901-9.

38. Prieto-Alamo MJ, Laval F. Deficient DNA-ligase activity in the metabolic disease tyrosinemia type I. Proc Natl Acad Sci U S A [Internet]. 1998 Oct 13 [cited 2017 Oct 27];95(21):12614-8. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC22879

39. Rosenberg LE, Segal S. Maleic acid-induced inhibition of amino acid transport in rat kidney. Biochem J [Internet]. 1964 Aug [cited 2017 Oct 27];92(2):345-52. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1206001

40. Worthen HG. Renal toxicity of maleic acid in the rat: enzymatic and morphologic observations. Lab Invest. 1963 Aug;12:791-801.

41. Eiam-ong S, Spohn M, Kurtzman NA, Sabatini S. Insights into the biochemical mechanism of maleic acid-induced Fanconi syndrome. Kidney Int. 1995 Nov;48(5):1542-8.

42. Sassa S, Kappas A. Hereditary tyrosinemia and the heme biosynthetic pathway. Profound inhibition of delta-aminolevulinic acid dehydratase activity by succinylacetone. J Clin Invest [Internet]. 1983 Mar [cited 2017 Oct 27];71(3):625-34. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC436912

43. Felitsyn N, McLeod C, Shroads AL, Stacpoole PW, Notterpek L. The heme precursor delta-aminolevulinate blocks peripheral myelin formation. J Neurochem [Internet]. 2008 Sep [cited 2017 Oct 27];106(5):2068-79. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2574579

44. Grenier A, Lescault A, Laberge C, Gagne R, Mamer O. Detection of succinylacetone and the use of its measurement in mass screening for hereditary tyrosinemia. Clin Chim Acta. 1982 Aug 4;123(1-2):93-9.

45. Cassiman D, Zeevaert R, Holme E, Kvittingen EA, Jaeken J. A novel mutation causing mild, atypical fumarylacetoacetase deficiency (Tyrosinemia type I): a case report. Orphanet J Rare Dis [Internet]. 2009 Dec 15 [cited 2017 Oct 27];4:28. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2802351

46. Blackburn PR, Hickey RD, Nace RA, Giama NH, Kraft DL, Bordner AJ, et al. Silent tyrosinemia type I without elevated tyrosine or succinylacetone associated with liver cirrhosis and hepatocellular carcinoma. Hum Mutat [Internet]. 2016 Oct [cited 2017 Oct 27];37(10):1097-105. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC5108417

47. De Jesus V, Adam BW, Mandel D, Cuthbert CD, Matern D. Succinylacetone as primary marker to detect tyrosinemia type I in newborns and its measurement by newborn screening programs. Mol Genet Metab [Internet]. 2014 Sep [cited 2017 Oct 27];113(1-2):67-75. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4533100

48. Mayorandan S, Meyer U, Gokcay G, Segarra NG, de Baulny HO, van Spronsen F, et al. Cross-sectional study of 168 patients with hepatorenal tyrosinaemia and implications for clinical practice. Orphanet J Rare Dis [Internet]. 2014 Aug 1 [cited 2017 Oct 27];9:107. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4347563

49. Han LS, Ye J, Qiu WJ, Zhang HW, Wang Y, Ji WJ, et al. [Application of succinylacetone levels measurement in the blood and urine in the diagnosis of tyrosinemia type 1]. Zhonghua Er Ke Za Zhi. 2012 Feb;50(2):126-30. Chinese.

50. Maheshwar Reddy G, Jayanthi U, Girish HR, Subhashini P, Sushma N. Is succinylacetone a pathognomonic marker for diagnosing tyrosinemia type 1? Int J Sci Eng Res. 2017;4(8).

51. Avery ME, Clow CL, Menkes JH, Ramos A, Scriver CR, Stern L, et al. Transient tyrosinemia of the newborn: dietary and clinical aspects. Pediatrics. 1967 Mar;39(3):378-84.

52. Goulden KJ, Moss MA, Cole DE, Tithecott GA, Crocker JF. Pitfalls in the initial diagnosis of tyrosinemia: three case reports and a review of the literature. Clin Biochem. 1987 Jun;20(3):207-12.

53. Hutchesson AC, Hall SK, Preece MA, Green A. Screening for tyrosinaemia type I. Arch Dis Child Fetal Neonatal Ed [Internet]. 1996 May [cited 2017 Oct 27];74(3):F191-F194. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2528336

54. la Marca G, Malvagia S, Pasquini E, Innocenti M, Fernandez MR, Donati MA, et al. The inclusion of succinylacetone as marker for tyrosinemia type I in expanded newborn screening programs. Rapid Commun Mass Spectrom. 2008;22(6):812-8.

55. la Marca G, Malvagia S, Pasquini E, Cavicchi C, Morrone A, Ciani F, et al. Newborn screening for tyrosinemia type I: further evidence that succinylacetone determination on blood spot is essential. JIMD Rep [Internet]. 2011 [cited 2017 Oct 27];1:107-9. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3509819

56. Morris AF, Holton JB, Burman D, Colley JR. Phenylalanine and tyrosine levels in newborn screening blood samples. Arch Dis Child [Internet]. 1983 Apr [cited 2017 Oct 27];58(4):271-5. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1627947

57. Rehak A, Selim MM, Yadav G. Richner-Hanhart syndrome (tyrosinaemia-II) (report of four cases without ocular involvement). Br J Dermatol. 1981 Apr;104(4):469-75.

58. Bienfang DC, Kuwabara T, Pueschel SM. The Richner-Hanhart syndrome: report of a case with associated tyrosinemia. Arch Ophthalmol. 1976 Jul;94(7):1133-7.

59. Paige DG, Clayton P, Bowron A, Harper JI. Richner-Hanhart syndrome (oculocutaneous tyrosinaemia, tyrosinaemia type II). J R Soc Med [Internet]. 1992 Dec [cited 2017 Oct 27];85(12):759-60. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1293768

60. Tsai CP, Lin PY, Lee NC, Niu DM, Lee SM, Hsu WM. Corneal lesion as the initial manifestation of tyrosinemia type II. J Chin Med Assoc. 2006 Jun;69(6):286-8.

61. Ahmad S, Teckman JH, Lueder GT. Corneal opacities associated with NTBC treatment. Am J Ophthalmol. 2002 Aug;134(2):266-8.

62. Wisse RP, Wittebol-Post D, Visser G, van der Lelij A. Corneal depositions in tyrosinaemia type I during treatment with Nitisinone. BMJ Case Rep [Internet]. 2012 Nov 30 [cited 2017 Oct 27];2012. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4543320

63. Gissen P, Preece MA, Willshaw HA, McKiernan PJ. Ophthalmic follow-up of patients with tyrosinaemia type I on NTBC. J Inherit Metab Dis. 2003;26(1):13-6.